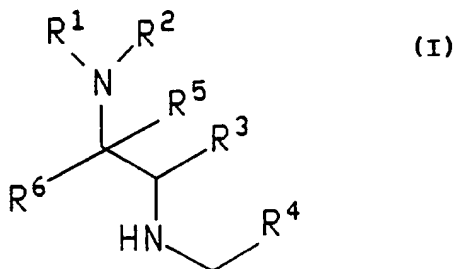




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : C07C 217/58, C07D 295/125, 209/48 A61K 31/135, C07D 295/12	A1	(11) International Publication Number: WO 93/10073 (43) International Publication Date: 27 May 1993 (27.05.93)
(21) International Application Number: PCT/US92/07730 (22) International Filing Date: 18 September 1992 (18.09.92) (30) Priority data: 790,934 12 November 1991 (12.11.91) US (60) Parent Application or Grant (63) Related by Continuation US 790,934 (CIP) Filed on 12 November 1991 (12.11.91) (71) Applicant (for all designated States except US): PFIZER INC. [US/US]; 235 East 42nd Street, New York, NY 10017 (US).		(72) Inventor; and (75) Inventor/Applicant (for US only): O'NEILL, Brian, T. [US/ US]; 1526 Essex Road, Westbrook, CT 06498 (US). (74) Agents: RICHARDSON, Peter, C. et al.; Pfizer Inc., Pa- tent Department, 235 East 42nd Street, New York, NY 10017 (US). (81) Designated States: AU, CA, FI, HU, JP, KR, NO, US, Eu- ropean patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, SE). Published <i>With international search report.</i>

(54) Title: ACYCLIC ETHYLENEDIAMINE DERIVATIVES AS SUBSTANCE P RECEPTOR ANTAGONISTS

**(57) Abstract**

The present invention relates to novel acyclic ethylenediamine derivatives of nitrogen containing heterocyclic compounds, and specifically, to compounds of formula (I) wherein R¹, R², R³, R⁴, R⁵ and R⁶ are defined as in the specification. It also relates to novel intermediates used in the synthesis of such derivatives. Compounds of formula (I) and their pharmaceutically acceptable salts are useful in the treatment of inflammatory and central nervous system disorders, as well as other disorders.

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ACYCLIC ETHYLENEDIAMINE DERIVATIVES AS SUBSTANCE P RECEPTOR ANTAGONISTS

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Background of the Invention

The present invention relates to novel acyclic ethylenediamine derivatives, pharmaceutical compositions comprising such compounds and the use of such compounds in the treatment and prevention of inflammatory and central nervous system disorders, as well as several other disorders. The pharmaceutically active compounds of this invention are substance P receptor antagonists. This invention also relates to novel intermediates used in the synthesis of such substance P receptor antagonists.

Substance P is a naturally occurring undecapeptide belonging to the tachykinin family of peptides, the latter being named because of their prompt stimulatory action on smooth muscle tissue. More specifically, substance P is a pharmacologically active neuropeptide that is produced in mammals (having originally been isolated from gut) and possesses a characteristic amino acid sequence that is illustrated by D. F. Veber et al. in U.S. Patent No. 4,680,283. The wide involvement of substance P and other tachykinins in the pathophysiology of numerous diseases has been amply demonstrated in the art. For instance, substance P has recently been shown to be involved in the transmission of pain or migraine (see B.E.B. Sandberg et al., Journal of Medicinal Chemistry, 25, 1009 (1982)), as well as in central nervous system disorders such as anxiety and schizophrenia, in respiratory and inflammatory diseases such as asthma and rheumatoid arthritis, respectively, in rheumatic diseases such as fibrositis, and in gastrointestinal disorders and diseases of the GI tract such as ulcerative colitis and Crohn's disease, etc. (see D. Regoli in "Trends in Cluster Headache," edited by F. Sicuteri et al., Elsevier Scientific Publishers, Amsterdam, pp. 85-95 (1987)).

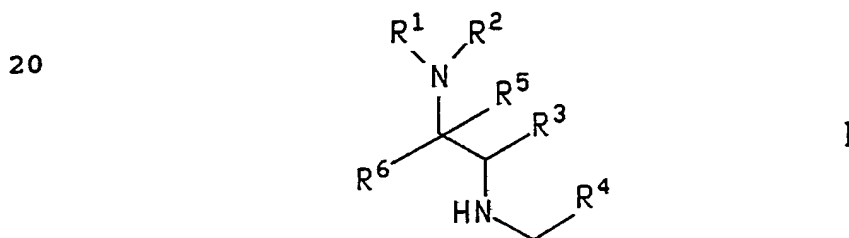
Quinuclidine, piperidine, azanorbornane derivatives and related compounds that exhibit activity as substance P

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receptor antagonists are referred to in United States Patent Application 566,338 filed November 20, 1989, United States Patent Application 724,268, filed July 1, 1991, PCT Patent Application PCT/US 91/02853, filed April 25, 1991, PCT
5 Patent Application PCT/US 91/03369, filed May 14, 1991, PCT Patent Application PCT/US 91/05776, filed August 20, 1991, PCT Patent Application PCT/US 92/00113, filed January 17, 1992, PCT Patent Application PCT/US 92/03571, filed May 5, 1992, PCT Patent Application PCT/US 92/03317, filed April
10 28, 1992, PCT Patent Application PCT/US 92/04697, filed June 11, 1992, United States Patent Application 766,488, filed September 26, 1991, United States Patent Application 790,934, filed November 12, 1991, PCT Patent Application PCT/US 92/04002, filed May 19, 1992, and Japanese Patent
15 Application No. 065337/92, filed March 23, 1992.

Summary of the Invention

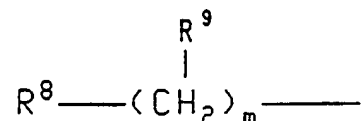
The present invention relates to compounds of the formula



25 wherein R¹ is hydrogen, (C₁-C₈) alkyl, a saturated (C₆-C₁₀) carbocyclic ring system containing two fused rings, a saturated (C₆-C₁₀) carbocyclic bridged ring system containing two rings, or benzyl wherein the phenyl moiety of said
30 benzyl may optionally be substituted with one or more substituents independently selected from halo, (C₁-C₆) alkyl optionally substituted with from one to three fluorine atoms and (C₁-C₈) alkoxy optionally substituted with from one to three fluorine atoms;

35 R² is hydrogen, benzyl or a group of the formula

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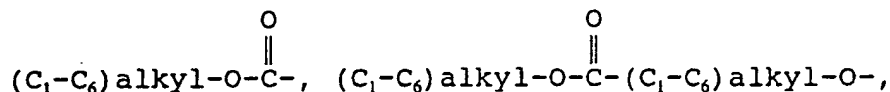
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wherein m is an integer from zero to twelve, and any one of the carbon-carbon single bonds of $(\text{CH}_2)_m$, wherein both carbon atoms of such bond are bonded to each other and to another carbon atom of the $(\text{CH}_2)_m$ chain, may optionally be replaced

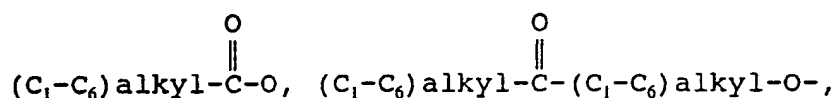
10 by a carbon-carbon double or triple bond, and any one of the carbon atoms of $(\text{CH}_2)_m$ may optionally be substituted with R^9 ;

R^8 and R^9 are independently selected from hydrogen, hydroxy, halo, amino, carboxy, carboxy $(\text{C}_1\text{-C}_6)$ alkyl, $(\text{C}_1\text{-C}_6)$ alkylamino, di- $(\text{C}_1\text{-C}_6)$ alkylamino, $(\text{C}_1\text{-C}_6)$ alkoxy,

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$(\text{C}_1\text{-C}_6)\text{alkyl-C}(=\text{O})\text{---}$, $(\text{C}_1\text{-C}_6)$ straight or branched alkyl, $(\text{C}_3\text{-C}_7)$ cycloalkyl wherein one of the carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; aryl selected from phenyl and naphthyl; heteroaryl selected from indanyl, thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; phenyl- $(\text{C}_2\text{-C}_6)$ alkyl, benzhydryl and benzyl, wherein each of said aryl and heteroaryl groups and the phenyl moieties of said benzyl, phenyl- $(\text{C}_2\text{-C}_6)$ alkyl and benzhydryl may optionally be substituted with one or two substituents independently

30 selected from halo, nitro, $(\text{C}_1\text{-C}_6)$ alkyl optionally substituted with from one to three fluorine atoms, $(\text{C}_1\text{-C}_6)$ alkoxy optionally substituted with from one to three

35

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fluorine atoms, amino, (C₁-C₆)-alkylamino, (C₁-C₆)alkyl-O-C(=O)-,
 5 (C₁-C₆)alkyl-O-C(=O)-(C₁-C₆)alkyl-, (C₁-C₆)alkyl-C(=O)-O-,
 10 (C₁-C₆)alkyl-C(=O)-(C₁-C₆)alkyl-O-, (C₁-C₆)alkyl-C(=O)-,
 15 (C₁-C₆)alkyl-C(=O)-(C₁-C₆)alkyl-, di-(C₁-C₆)alkylamino,
 20 -C(=O)NH-(C₁-C₆)alkyl, (C₁-C₆)-alkyl-C(=O)NH-(C₁-C₆)alkyl, -NHCH(=O) and

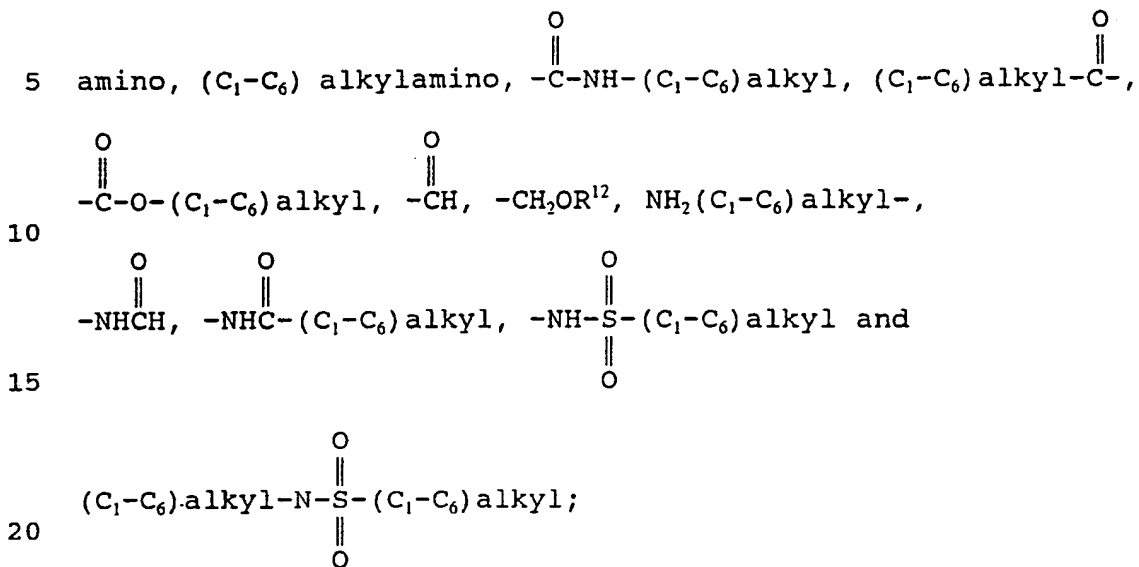
-NHC(=O)-(C₁-C₆)alkyl; and wherein one of the phenyl moieties of
 said benzhydryl may optionally be replaced by naphthyl,
 25 thienyl, furyl or pyridyl;

or R¹ and R², together with the nitrogen to which they
 are attached, form a saturated or unsaturated monocyclic
 ring containing from three to eight carbon atoms, a fused
 bicyclic ring containing from six to ten carbon atoms, or a
 30 saturated bridged ring system containing from six to ten
 carbon atoms;

R⁴ is aryl selected from phenyl and naphthyl; heteroaryl
 selected from indanyl, thienyl, furyl, pyridyl, thiazolyl,
 isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl
 35 and quinolyl; and cycloalkyl having from three to seven
 carbon atoms wherein one of said carbon atoms may optionally
 be replaced by nitrogen, oxygen or sulfur; wherein each of
 said aryl and heteroaryl groups may optionally be
 substituted with one or more substituents, and said (C₃-C₇)
 40 cycloalkyl may optionally be substituted with one, two or
 three substituents, each of said substituents being
 independently selected from halo, nitro, (C₁-C₆) alkyl
 optionally substituted with from one to three fluorine

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atoms, (C₁-C₆) alkoxy optionally substituted with from one to three fluorine atoms, phenyl,



R³ is hydrogen, (C₃-C₈) cycloalkyl, (C₁-C₆) straight or branched alkyl or phenyl optionally substituted with one or
 25 more substituents independently selected from halo, (C₁-C₆) alkyl optionally substituted with from one to three fluorine atoms, and (C₁-C₆) alkoxy optionally substituted with from one to three fluorine atoms;

R⁵ is hydrogen, (C₁-C₆) alkyl, or phenyl optionally
 30 substituted with one or more substituents independently selected from halo, (C₁-C₆) alkyl optionally substituted with from one to three fluorine atoms and (C₁-C₆) alkoxy optionally substituted with from one to three fluorine atoms;

R⁶ is selected from hydrogen, (C₁-C₆) straight or
 35 branched alkyl, (C₃-C₇) cycloalkyl wherein one of the carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; aryl selected from phenyl, biphenyl, indanyl and naphthyl; heteroaryl selected from thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl,
 40 tetrazolyl and quinolyl; phenyl (C₂-C₆) alkyl, benzhydryl and benzyl, wherein each of said aryl and heteroaryl groups and the phenyl moieties of said benzyl, phenyl (C₂-C₆) alkyl and benzhydryl may optionally be substituted with one or more

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substituents independently selected from halo, nitro, (C₁-C₆) alkyl optionally substituted with from one to three fluorine atoms, (C₁-C₆) alkoxy, trifluoromethyl, amino, trihaloalkoxy

5 (e.g., trifluoromethoxy), (C₁-C₆) alkylamino, (C₁-C₆) alkyl-O-C(=O)-,
 10 (C₁-C₆) alkyl-O-C(=O)-(C₁-C₆) alkyl, (C₁-C₆) alkyl-C(=O)-O-,
 15 (C₁-C₆) alkyl-C(=O)-(C₁-C₆) alkyl-O-, (C₁-C₆) alkyl-C(=O)-,
 (C₁-C₆) alkyl-C(=O)-(C₁-C₆) alkyl-, di-(C₁-C₆) alkylamino,
 20 -C(=O)NH-(C₁-C₆) alkyl, (C₁-C₆) alkyl-C(=O)NH-(C₁-C₆) alkyl-, -NHCH(=O) and
 25 -NHC(=O)-(C₁-C₆) alkyl; and wherein one of the phenyl moieties of
 said benzhydryl may optionally be replaced by naphthyl,
 thienyl, furyl or pyridyl; and

R¹² is hydrogen, (C₁-C₃) alkyl or phenyl.

Preferred compounds of the formula I include those
 30 wherein R² is hydrogen, or R² and R¹, together with the
 nitrogen to which they are attached, form a monocyclic ring
 containing five to seven carbon atoms; R³ is hydrogen, methyl
 or phenyl; R⁵ is hydrogen; R⁴ is phenyl or indanyl, wherein
 said phenyl or indanyl may optionally be substituted with
 35 from one to three substituents independently selected from
 halo, nitro, (C₁-C₆) alkyl optionally substituted with from
 one to three fluorine atoms, (C₁-C₆) alkoxy, trihaloalkoxy
 (e.g., trifluoromethoxy), (C₁-C₆) alkylamino, -C(=O)NH-(C₁-
 C₆) alkyl, (C₁-C₆) alkyl-C(=O)-, -C(=O)-O-(C₁-C₆) alkyl, -C(=O)H,
 40 -CH₂OR¹³, -NH(C₁-C₆) alkyl, -NHC(=O)H, -NHC(=O)-(C₁-C₆) alkyl,
 -NHSO₂(C₁-C₆) alkyl and (C₁-C₆) alkyl-N-SO₂-(C₁-C₆) alkyl; and R⁶ is
 phenyl.

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Particularly preferred compounds of the formula I are those wherein R¹ is alkyl, R⁶ is unsubstituted phenyl, R⁴ is a monosubstituted or disubstituted aryl group that is substituted at the C-2 position with an alkoxy group or substituted at the C-5 position with an alkyl, alkoxy or trihaloalkoxy group, or substituted in such manner at both C-2 and C-5 positions (i.e., with an alkoxy group at the C-2 position and an alkyl, alkoxy or trihaloalkoxy group at the C-5 position), and each of R², R³ and R⁵ is hydrogen.

10 Examples of preferred compounds of the formula I include:

1-N-cyclohexyl-1-phenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine;

1-N-cyclohexyl-1-phenyl-2-N'-[(2-methoxy-5-trifluoromethoxyphenyl)methyl]-1,2-ethanediamine;

1-N-pyrrolidyl-1-phenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine;

1-N-methyl-1-phenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine;

20 1-N-cyclopentyl-1-phenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine;

1-N-propyl-1-phenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine;

1-N-phenylmethyl-1-phenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine;

25 1-N-cyclooctyl-1-phenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine;

1-N-cyclobutyl-1-phenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine;

30 1-N-(2-adamantyl)-1-phenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine;

1-N-(1,1-dimethylethyl)-1-phenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine;

1-N-cyclopropyl-1-phenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine;

35 1-N-isopropyl-1-phenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine;

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1-N-(1-phenylethyl)-1-phenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine;

1-N-(2-norbornyl)-1-phenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine;

5 1-N-cyclohexyl-1-phenyl-2-N'-[(2-methoxy-5-tert-butylphenyl)methyl]-1,2-ethanediamine;

1-N-cyclohexyl-1-phenyl-2-N'-[(2-methoxy-5-isopropylphenyl)methyl]-1,2-ethanediamine;

10 1-N-cyclohexyl-1-phenyl-2-N'-[(2-methoxy-4,5-dimethylphenyl)methyl]-1,2-ethanediamine; and

1-N-cyclohexyl-1-N-(6-hydroxyhexyl)-1-phenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine.

Other compounds of the formula I include:

15 1-N-phenyl-1-phenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine;

1-N-(2-aza-bicyclo[4.4.0]decane)-1-phenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine;

1,1-diphenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine;

20 1,1-diphenyl-2-N'-[(2,5-dimethoxyphenyl)methyl]-1,2-ethanediamine;

1,1-diphenyl-2-N'-[(2,4-dimethoxyphenyl)methyl]-1,2-ethanediamine;

25 1-N-cyclohexyl-1-N-(6-n-hexanol)-1-phenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine;

1-N-cyclohexyl-1-N-(3-phenylpropyl)-1-phenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine;

3,3-diphenyl-2-N-cyclopentyl-1-N'-[(2-methoxyphenyl)methyl]-1,2-propanediamine;

30 1-N-(2-phenylethyl)-1-(3,4-methylenedioxyphenyl)-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine;

1-N-cyclopentyl-1-(2-naphthyl)-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine;

35 1-N-cyclohexyl-1-cyclohexyl-1-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine;

1-cyclohexylamino-1-phenyl-2-[(2-methoxyphenyl)methyl-amino]propane;

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- 1-N-pyrrolidyl-1-phenyl-2-[(2-methoxyphenyl)methyl-
amino]propane;
1-N-piperidyl-1-phenyl-2-[(2-methoxyphenyl)methyl-
amino]propane;
5 1-cyclopentylamino-1-phenyl-2-[(2-methoxyphenyl)methyl-
amino]propane;
1-cyclooctylamino-1-phenyl-2-[(2-methoxyphenyl)methyl-
amino]propane;
1-propylamino-1-phenyl-2-[(2-methoxyphenyl)methylamino]
10 propane;
1-amino-1-phenyl-2-[(2-methoxyphenyl)methylamino]-3-
methoxypropane;
1-methylamino-1-phenyl-2-[(2-methoxyphenyl)methyl-
amino]-3-methoxypropane;
15 1-cycloheptylamino-1-phenyl-2-[(2-methoxyphenyl)methyl-
amino]propane;
1-amino-1-phenyl-2-[(2-methoxyphenyl)methyl-
amino]propane;
1-(4-pyranyl)amino-1-phenyl-2-[(2-methoxyphenyl)methyl-
20 amino]propane;
1-N-cyclopentyl-1-phenyl-2-N'-[(2-methoxy-5-tert-
butylphenyl)methyl]-1,2-ethanediamine;
1-N-methyl-1-phenyl-2-N'-[(2-methoxy-5-tert-
butylphenyl)methyl]-1,2-ethanediamine;
25 1-N-cyclopentyl-1-phenyl-2-N'-[(2-methoxy-5-
isopropylphenyl)methyl]-1,2-ethanediamine;
1-N-methyl-1-phenyl-2-N'-[(2-methoxy-5-
isopropylphenyl)methyl]-1,2-ethanediamine;
1-N-cyclopentyl-1-phenyl-2-N'-[(2-methoxy-4,5-
30 dimethylphenyl)methyl]-1,2-ethanediamine;
1-N-methyl-1-phenyl-2-N'-[(2-methoxy-4,5-
dimethylphenyl)methyl]-1,2-ethanediamine;
1-N-cyclohexyl-1-phenyl-2-N'-[(2-methoxy-5-
(methylamino-N-methanesulfonamide)phenyl)methyl]-1,2-
35 ethanediamine;
1-N-methyl-1-phenyl-2-N'-[(2-methoxy-5-(methylamino-N-
methanesulfonamide)phenyl)methyl]-1,2-ethanediamine;

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1-N-cyclopentyl-1-phenyl-2-N'-[(2-methoxy-5-(methylamino-N-methanesulfonamide)phenyl)methyl]-1,2-ethanediamine;

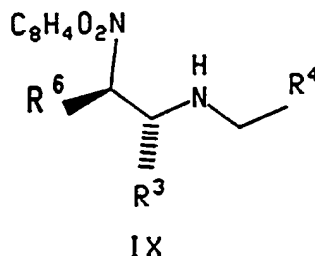
1-N-cyclohexyl-1-phenyl-2-N'-[(2-methoxy-5-(2-propylamino-N-methanesulfonamide)phenyl)methyl]-1,2-ethanediamine;

1-N-methyl-1-phenyl-2-N'-[(2-methoxy-5-(2-propylamino-N-methanesulfonamide)phenyl)methyl]-1,2-ethanediamine; and

1-N-cyclopentyl-1-phenyl-2-N'-[(2-methoxy-5-(2-propylamino-N-methanesulfonamide)phenyl)methyl]-1,2-ethanediamine.

The present invention also relates to the pharmaceutically acceptable acid addition salts of compounds of the formula I. The acids which are used to prepare the pharmaceutically acceptable acid addition salts of the aforementioned base compounds of this invention are those which form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, acetate, lactate, citrate, acid citrate, tartrate, bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)] salts.

The present invention also relates to compounds of the formula



wherein R^3 , R^4 , and R^6 are defined as for formula I. These compounds are useful as intermediates in the synthesis of compounds of the formula I.

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The term "halo", as used herein, unless otherwise indicated, includes chloro, fluoro, bromo and iodo.

The term "alkyl", as used herein, unless otherwise indicated, includes saturated monovalent hydrocarbon radicals having straight, branched or cyclic moieties or combinations thereof.

The term "alkoxy," as used herein, includes -O-alkyl groups wherein "alkyl" is defined as above.

The term "one or more substituents," as used herein, includes from one to the maximum number of substituents possible based on the number of available bonding sites.

The present invention also relates to a pharmaceutical composition for treating or preventing a condition selected from the group consisting of inflammatory diseases (e.g., arthritis, psoriasis, asthma and inflammatory bowel disease), anxiety, depression or dysthymic disorders, colitis, psychosis, pain, allergies such as eczema and rhinitis, chronic obstructive airways disease, hypersensitivity disorders such as poison ivy, vasospastic diseases such as angina, migraine and Reynaud's disease, fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis, reflex sympathetic dystrophy such as shoulder/hand syndrome, addiction disorders such as alcoholism, stress related somatic disorders, peripheral neuropathy, neuralgia, neuropathological disorders such as Alzheimer's disease, AIDS related dementia, diabetic neuropathy and multiple sclerosis, disorders related to immune enhancement or suppression such as systemic lupus erythematosus, and rheumatic diseases such as fibrositis in a mammal, including a human, comprising an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, effective in treating or preventing such condition, and a pharmaceutically acceptable carrier.

The present invention also relates to a method of treating or preventing a condition selected from the group consisting of inflammatory diseases (e.g., arthritis, psoriasis, asthma and inflammatory bowel disease), anxiety,

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depression or dysthymic disorders, colitis, psychosis, pain, allergies such as eczema and rhinitis, chronic obstructive airways disease, hypersensitivity disorders such as poison ivy, vasospastic diseases such as angina, migraine and
5 Reynaud's disease, fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis, reflex sympathetic dystrophy such as shoulder/hand syndrome, addiction disorders such as alcoholism, stress related somatic disorders, peripheral neuropathy, neuralgia,
10 neuropathological disorders such as Alzheimer's disease, AIDS related dementia, diabetic neuropathy and multiple sclerosis, disorders related to immune enhancement or suppression such as systemic lupus erythematosus, and
15 a human, comprising administering to said mammal an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, effective in treating or preventing such condition.

The present invention also relates to a pharmaceutical
20 composition for antagonizing the effects of substance P in a mammal, including a human, comprising a substance P antagonizing amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

25 The present invention also relates to a method of antagonizing the effects of substance P in a mammal, including a human, comprising administering to said mammal
* a substance P antagonizing amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof.

30 The present invention also relates to a pharmaceutical composition for treating or preventing a disorder in a mammal, including a human, resulting from an excess of substance P, comprising a substance P antagonizing amount of a compound of the formula I, or a pharmaceutically
35 acceptable salt thereof, and a pharmaceutically acceptable carrier.

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The present invention also relates to a method of treating or preventing a disorder in a mammal, including a human, resulting from an excess of substance P, comprising administering to said mammal a substance P antagonizing amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof.

The present invention also relates to a pharmaceutical composition for treating or preventing a condition selected from the group consisting of inflammatory diseases (e.g., arthritis, psoriasis, asthma and inflammatory bowel disease), anxiety, depression or dysthymic disorders, colitis, psychosis, pain, allergies such as eczema and rhinitis, chronic obstructive airways disease, hypersensitivity disorders such as poison ivy, vasospastic diseases such as angina, migraine and Reynaud's disease, fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis, reflex sympathetic dystrophy such as shoulder/hand syndrome, addiction disorders such as alcoholism, stress related somatic disorders, peripheral neuropathy, neuralgia, neuropathological disorders such as Alzheimer's disease, AIDS related dementia, diabetic neuropathy and multiple sclerosis, disorders related to immune enhancement or suppression such as systemic lupus erythematosus, and rheumatic diseases such as fibrositis in a mammal, including a human, comprising an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, effective in antagonizing the effect of substance P at its receptor site, and a pharmaceutically acceptable carrier.

The present invention also relates to a method of treating or preventing a condition selected from the group consisting of inflammatory diseases (e.g., arthritis, psoriasis, asthma and inflammatory bowel disease), anxiety, depression or dysthymic disorders, colitis, psychosis, pain, allergies such as eczema and rhinitis, chronic obstructive airways disease, hypersensitivity disorders such as poison ivy, vasospastic diseases such as angina, migraine and

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Reynaud's disease, fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis, reflex sympathetic dystrophy such as shoulder/hand syndrome, addiction disorders such as alcoholism, stress related
5 somatic disorders, peripheral neuropathy, neuralgia, neuropathological disorders such as Alzheimer's disease, AIDS related dementia, diabetic neuropathy and multiple sclerosis, disorders related to immune enhancement or suppression such as systemic lupus erythematosus, and
10 rheumatic diseases such as fibrositis in a mammal, including a human, comprising administering to said mammal an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, effective in antagonizing the effect of substance P at its receptor site.

15 The present invention also relates to a pharmaceutical composition for treating or preventing a disorder in a mammal, including a human, the treatment or prevention of which is effected or facilitated by a decrease in substance P mediated neurotransmission, comprising an amount of a
20 compound of the formula I, or a pharmaceutically acceptable salt thereof, effective in antagonizing the effect of substance P at its receptor site, and a pharmaceutically acceptable carrier.

The present invention also relates to a method of
25 treating or preventing a disorder in mammal, including a human, the treatment or prevention of which is effected or facilitated by a decrease in substance P mediated neurotransmission, comprising administering to said mammal an amount of a compound of the formula I, or a
30 pharmaceutically acceptable salt thereof, effective in antagonizing the effect of substance P at its receptor site.

The present invention also relates to a pharmaceutical composition for treating or preventing a disorder in a mammal, including a human, the treatment or prevention of
35 which is effected or facilitated by a decrease in substance P mediated neurotransmission, comprising an amount of a compound of the formula I, or a pharmaceutically acceptable

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salt thereof, effective in treating or preventing such disorder, and a pharmaceutically acceptable carrier.

The present invention also relates to a method of treating or preventing a disorder in mammal, including a human, the treatment or prevention of which is effected or facilitated by a decrease in substance P mediated neurotransmission, comprising administering to said mammal an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, effective in treating or preventing such disorder.

The compounds of the formulae I and IX have chiral centers and therefore exist in different enantiomeric forms. This invention relates to all optical isomers and all stereoisomers of compounds of the formulae I and IX, and mixtures thereof.

In addition to their utility as substance P receptor antagonists, the novel optically active compounds of the formula I are also useful as starting materials in the preparation of the corresponding racemic mixture and opposite enantiomer.

Formulae I and IX above include compounds identical to those depicted but for the fact that one or more hydrogen, nitrogen or carbon atoms are replaced by isotopes thereof (e.g., tritium, nitrogen-15, carbon-14 or carbon-11 isotopes thereof). Such compounds are useful as research and diagnostic tools in metabolism pharmacokinetic studies and in binding assays. Specific applications in research include radioligand binding assays, autoradiography studies and in vivo binding studies, while specific applications in the diagnostic area include studies of the substance P receptor in the human brain in in vivo binding in the relevant tissues for inflammation, e.g. immune-type cells or cells that are directly involved in inflammatory bowel disorders and the like.

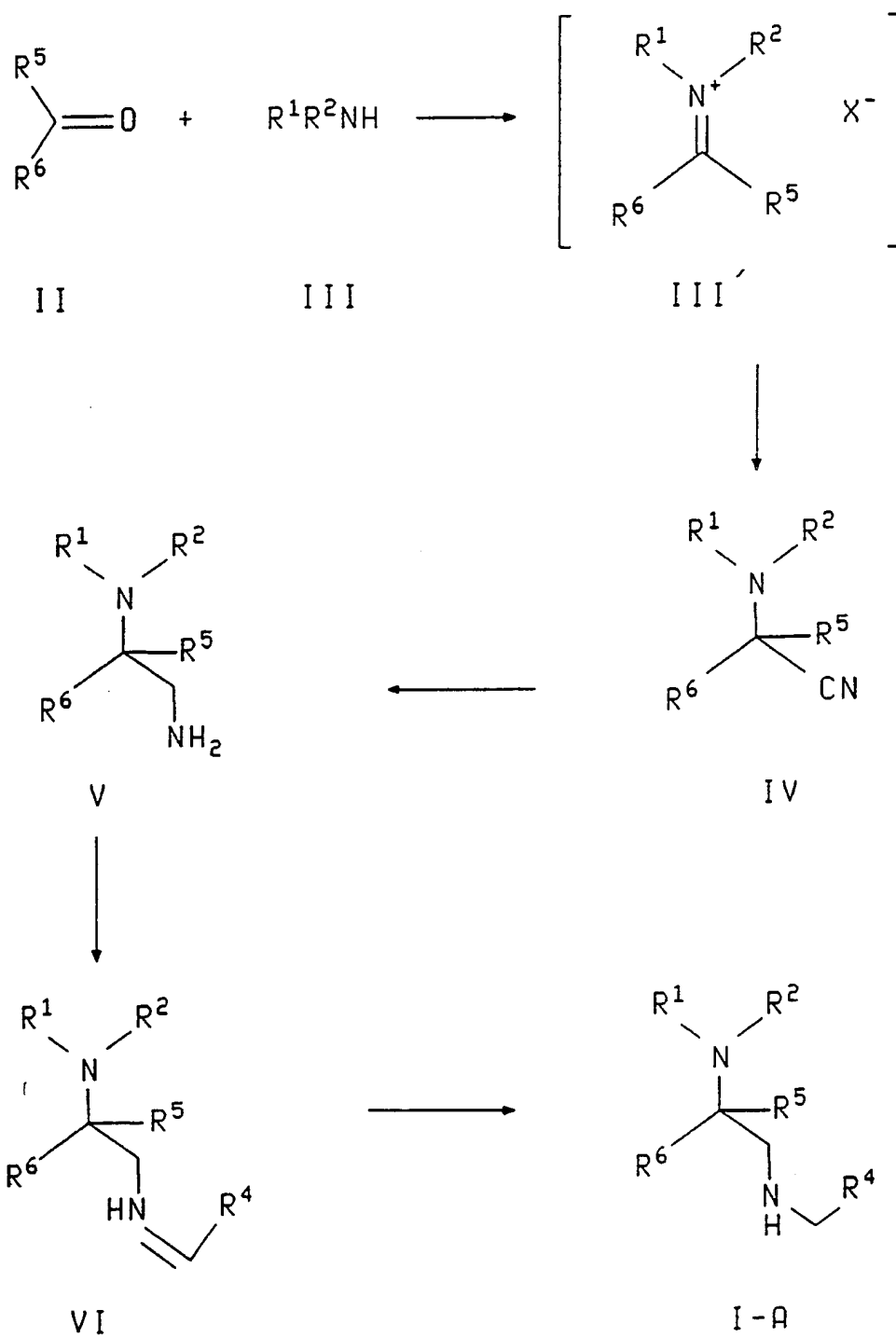
Detailed Description of the Invention

The compounds of the formula I may be prepared as described in the following reaction schemes and discussion.

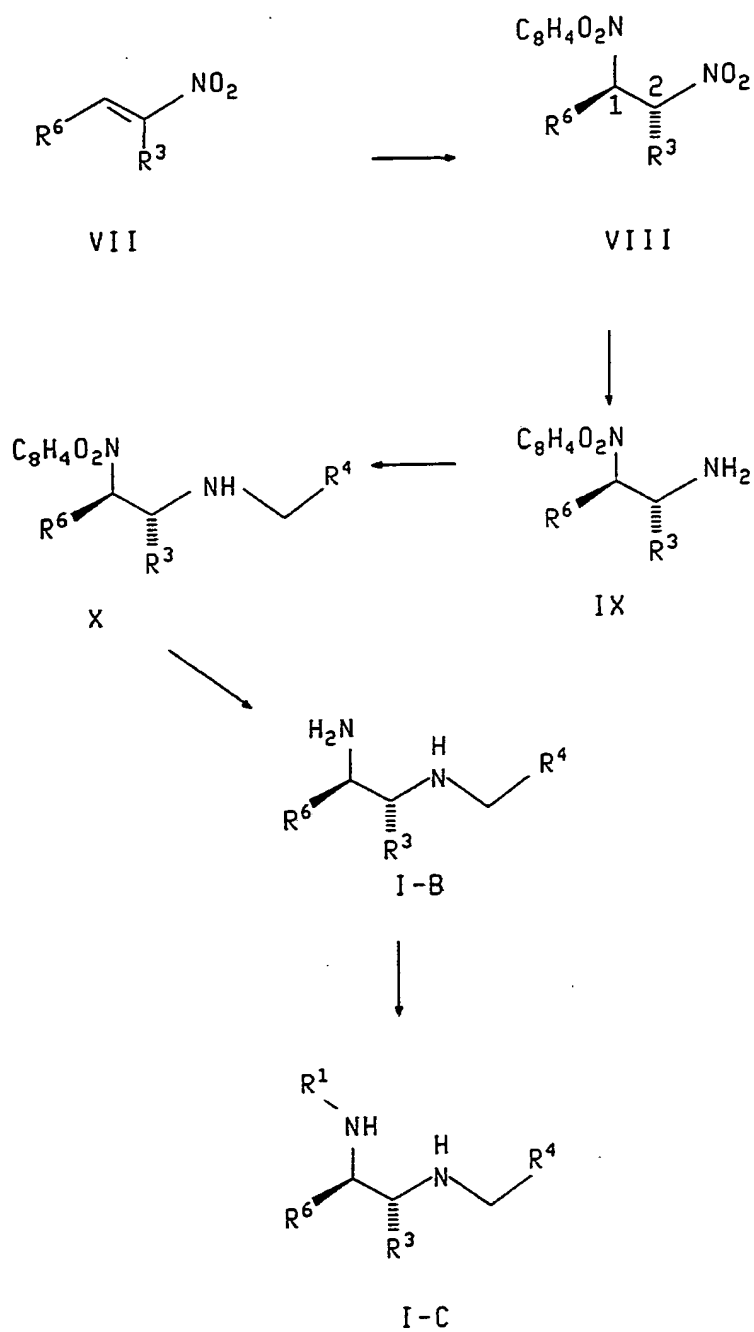
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Unless otherwise indicated, R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} and R^{13} , and structural formulae I and IX in the reaction schemes and discussion that follow are defined as above.

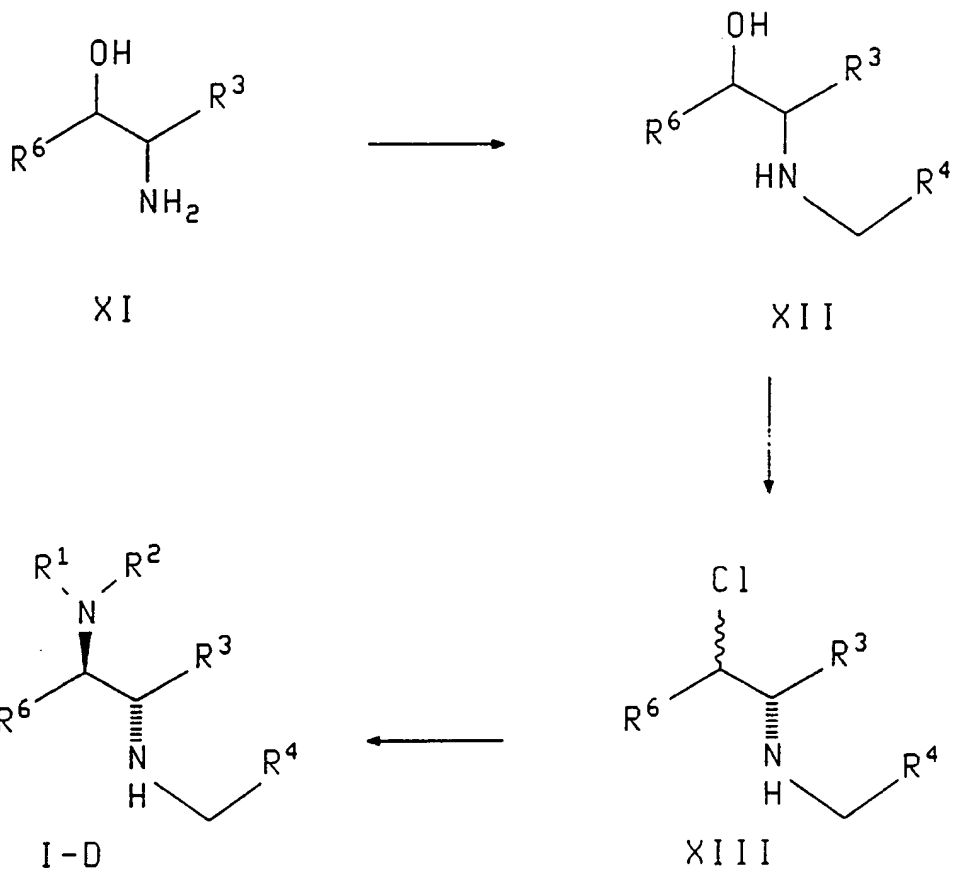
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Scheme 1

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Scheme 2

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Scheme 3

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5 Scheme 1 illustrates the preparation of compounds of the formula I.

Referring to scheme 1, a compound of the formula II is reacted with a compound of the formula III and a cyanide salt (e.g., potassium cyanide, sodium cyanide or
10 trimethylsilyl cyanide) to yield the corresponding compound of formula IV. The cyanide salt, which is preferably potassium cyanide, is added last. The reaction is typically conducted in the presence of acid catalyst in an inert aqueous solvent such as methanol/water, tetrahydrofuran
15 (THF)/water or acetonitrile/water, at a temperature from about 0°C to about 40°C. It is preferably conducted in methanol/water at about room temperature. Acid catalysts that may be used include sodium bisulfite, potassium bisulfite, sodium biphosphate, acetic acid and hydrochloric
20 acid. Sodium bisulfite is preferred. When trimethylsilyl cyanide is used, however, the reaction is preferably carried out neat or in THF, either in the absence of a catalyst or using zinc iodide as a catalyst.

The above reaction proceeds via an intermediate of the
25 formula III' which is formed in situ. Alternatively, the intermediate may be formed in a separate step, isolated, and then reacted with a cyanide salt to form the corresponding compound of formula IV. This procedure is preferably carried out by reacting the compounds formula II and III
30 under dehydrating conditions (e.g. in the presence of a titanium chloride catalyst or a dehydrating agent or using a Dean Stark trap) at a temperature from about 0°C to about 40°C. Suitable solvents include benzene, toluene, methylene chloride and chloroform.

35 Reduction of the resulting nitrile having formula IV produces the corresponding diamine of formula V. The reduction is generally accomplished using diisobutylaluminum hydride, borane-THF, dimethylsulfide, lithium aluminum hydride or aluminum hydride, preferably diisobutylaluminum
40 hydride. Suitable solvents include nonpolar solvents such as toluene, hexanes, petroleum ether and xylene. Toluene is

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preferred. The reaction temperature may range from about -78°C to about 0°C, and is preferably between about -26°C and 1°C.

The compound of formula V formed in the above step is

5 then reacted with a compound of the formula $R^1\overset{\overset{O}{||}}{C}H$ to produce the corresponding compound of formula VI. This reaction is generally carried out in an inert solvent such as benzene, 10 toluene or another solvent that separates water (e.g., using a Dean-Stark trap), or in an inert solvent such as THF or methylene chloride in the presence of a drying agent (e.g., using molecular sieves). Suitable temperatures for this reaction range from about 25°C to about 111°C. The reflux 15 temperature of the solvent is preferred.

The resulting imine of formula VI may be converted to the corresponding compound of the formula I-A by reacting it with a reducing agent. Suitable reducing agents include sodium borohydride, hydrogen and a metal catalyst, sodium 20 triacetoxymethylborohydride, sodium cyanoborohydride, zinc and hydrochloric acid, and formic acid. Sodium triacetoxymethylborohydride is preferred. This reduction is usually conducted in an inert solvent such as dichloroethane (DCE), dichloromethane (DCM), THF, methylene chloride, a 25 lower alcohol, chloroform or acetic acid, preferably acetic acid, at a temperature from about -20°C to about 60°C, preferably about room temperature.

Alternatively and preferably, reactions $V \rightarrow VI \rightarrow I-A$ described above are carried out as one step without 30 isolating the imine of formula VI. This procedure is illustrated in Example IC.

Scheme 2 illustrates the synthesis of compounds of the formula I wherein R^1 , R^2 and R^3 are hydrogen, having the depicted relative stereochemistry, i.e., the 1-(R,S)-2-(R,S) 35 configuration as defined by the Cahn-Ingold-Prelog system (hereinafter referred to as compounds of the formula I-B), and compounds of the formula I wherein R^1 is (C_1-C_8) alkyl, R^3

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and R^2 are hydrogen, having the depicted relative stereochemistry, i.e., 1-(R,S)-2-(R,S) configuration as defined by the Cahn-Ingold-Prelog system (hereinafter referred to as compounds of the formula I-C). For
5 convenience, only one enantiomer is depicted in scheme 2 for each of formulae VIII, IX, X, I-B and I-C. However, the procedure illustrated in scheme 2 applies to both enantiomers of these compounds.

Referring to scheme 2, a compound of the formula VII is
10 reacted with phthalimide in the presence of a base. Generally, a reaction inert solvent such as THF or a lower alcohol is used. Examples of appropriate bases are sodium and potassium hydroxides and hydrides, lithium diisopropylamide (LDA), 1,8-diazabicyclo[5.4.0] undec-7-ene
15 (DBU) and lithium hexamethyldisilane. The reaction temperature may range from about 0°C to about 100°C. Preferably, the compound of formula VII is reacted with phthalamide in ethanol in the presence of potassium hydroxide at about room temperature.

20 The above reaction produces a mixture of isomers containing the corresponding compound of the formula VIII, and its C-2 epimer. Crystallization from isopropyl ether yields the compound of formula VIII as the racemate of a single epimer, which is then reduced to produce the
25 corresponding compound of formula IX. Suitable reducing agents include Raney nickel/hydrogen, 10% palladium on charcoal/hydrogen, and aluminum amalgam. Preferably, the reduction is carried out using Raney nickel in ethanol under a hydrogen gas pressure of about 3 atm and at a temperature
30 of about 25°C. Temperatures from about 10°C to about 60°C and pressures from about 1 to about 10 atmospheres are also suitable.

Reductive amination of the compound of formula IX from the above step with sodium cyanoborohydride or sodium
35 triacetoxyborohydride and a compound of the formula $R^4\text{CHO}$ yields the corresponding compound of formula X. This reaction is typically carried out in a polar solvent such as

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acetic acid or a lower alkanol, at a temperature from about 0°C to about 50°C. Acetic acid is the preferred solvent and about 25°C is the preferred temperature. It is also preferable that the pH of the reaction mixture be about 4 to
5 about 5.

Alternatively, compounds of the formula IX may be converted to the corresponding compounds of the formula X by the two step procedure described above and illustrated in scheme 1 for converting compounds of the formula V into
10 compounds of the formula I-A ($V \rightarrow VI \rightarrow I-A$).

The corresponding compound of formula I-B is then prepared by reacting the compound of formula X from the above step with hydrazine. Usually, this is accomplished using an inert solvent such as a lower (C_1-C_4) alcohol, water
15 or a mixture of water and a lower alcohol, preferably ethanol, at a temperature from about 20°C to about the reflux temperature of the solvent, preferably at about the reflux temperature.

The resulting compound of formula I-B may be converted
20 into a compound of the formula I-C by reacting it with a ketone or aldehyde of the formula $R^{10}COR^{11}$, wherein R^{10} is hydrogen or alkyl and R^{11} is alkyl, so that in the resulting compound of formula I-C, $R^1 = CHR^{10}R^{11}$. This transformation is generally carried out using one of the procedures described
25 above for converting compounds of the formula V into compounds of the formula I-A. Thus, compounds of the formula I-C may be prepared by a two step procedure analogous to the reaction sequence $V \rightarrow VI \rightarrow I-A$ described above, in which an imine is formed in the first step, isolated and
30 treated with a reducing agent, or by the equivalent one step procedure in which the imine is formed in situ.

The preparation of compounds of the formula I wherein R^5 and one of R^1 and R^2 is hydrogen, having the depicted relative stereochemistry, ie., the 1-(R,S)-2-(S,R)
35 configuration as defined under the Cahn-Ingold-Prelog system (hereinafter referred to as compounds of the formula I-D) is illustrated in scheme 3.

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Referring to scheme 3, the desired R^4 group can be added to the compound of formula XI to form the corresponding compound having formula XII by the one step reductive amination described above for reaction $IX \rightarrow X$ of scheme 2 or the one step procedure resulting from combining reactions $V \rightarrow VI$ and $VI \rightarrow I-A$ in scheme I.

Reaction of the hydrochloride salt of the compound of formula XII so formed with a suitable chlorinating agent yields the corresponding compound of formula XIII. Examples chlorinating agents that may be used are thionyl chloride, phosphorous pentachloride, phosphorus oxychloride and mesyl chloride. This reaction is typically carried out neat or in an inert nonhydroxylic solvent such as methylene chloride, chloroform, 1,2-dichloroethane, benzene or toluene, preferably chloroform, at a temperature from about -2°C to about 15°C , preferably from about 0°C to about 5°C .

The corresponding compound of formula I-D can then be prepared as follows. The compound of formula XIII obtained in the preceding step is reacted with a compound of the formula $R^1R^2\text{NH}$. This reaction is generally conducted neat or in an inert solvent such as water, THF, tert-butanol, ethanol, dimethylether or acetonitrile, methanol, isopropanol, preferably ethanol, at a temperature from about 0°C to about the reflux temperature of the solvent, preferably at about the reflux temperature.

The preparation of other compounds of the formula I not specifically described in the foregoing experimental section can be accomplished using combinations of the reactions described above that will be apparent to those skilled in the art.

In each of the reactions discussed or illustrated in schemes 1 to 3 above, pressure is not critical unless otherwise indicated. Pressures from about 0.5 atmospheres to about 5 atmospheres are generally acceptable, and ambient pressure, i.e. about 1 atmosphere, is preferred as a matter of convenience.

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The novel compounds of the formula I and the pharmaceutically acceptable salts thereof are useful as substance P antagonists, i.e., they possess the ability to antagonize the effects of substance P at its receptor site in mammals, and therefore they are able to function as therapeutic agents in the treatment of the aforementioned disorders and diseases in an afflicted mammal.

The compounds of the formula I which are basic in nature are capable of forming a wide variety of different salts with various inorganic and organic acids. Although such salts must be pharmaceutically acceptable for administration to animals, it is often desirable in practice to initially isolate a compound of the Formula I from the reaction mixture as a pharmaceutically unacceptable salt and then simply convert the latter back to the free base compound by treatment with an alkaline reagent and subsequently convert the latter free base to a pharmaceutically acceptable acid addition salt. The acid addition salts of the base compounds of this invention are readily prepared by treating the base compound with a substantially equivalent amount of the chosen mineral or organic acid in an aqueous solvent medium or in a suitable organic solvent, such as methanol or ethanol. Upon careful evaporation of the solvent, the desired solid salt is readily obtained.

The compounds of formula I and their pharmaceutically acceptable salts exhibit substance P receptor-binding activity and therefore are of value in the treatment and prevention of a wide variety of clinical conditions the treatment or prevention of which are effected or facilitated by a decrease in substance P mediated neurotransmission. Such conditions include inflammatory diseases (e.g., arthritis, psoriasis, asthma and inflammatory bowel disease), anxiety, depression or dysthymic disorders, colitis, psychosis, pain, allergies such as eczema and rhinitis, chronic obstructive airways disease, hypersensitivity disorders such as poison ivy, vasospastic

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diseases such as angina, migraine and Reynaud's disease, fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis, reflex sympathetic dystrophy such as shoulder/hand syndrome, addiction disorders such as
5 alcoholism, stress related somatic disorders, peripheral neuropathy, neuralgia, neuropathological disorders such as Alzheimer's disease, AIDS related dementia, diabetic neuropathy and multiple sclerosis, disorders related to immune enhancement or suppression such as systemic lupus
10 erythematosus, and rheumatic diseases such as fibrositis. Hence, these compounds are readily adapted to therapeutic use as substance P antagonists for the control and/or treatment of any of the aforesaid clinical conditions in mammals, including humans.

15 The compounds of the formula I and the pharmaceutically acceptable salts thereof can be administered via either the oral, parenteral or topical routes. In general, these compounds are most desirably administered in dosages ranging from about 1.0 mg up to about 1500 mg per day, although
20 variations will necessarily occur depending upon the weight and condition of the subject being treated and the particular route of administration chosen. However, a dosage level that is in the range of about 0.07 mg to about 21 mg per kg of body weight per day is most desirably
25 employed. Variations may nevertheless occur depending upon the species of animal being treated and its individual response to said medicament, as well as on the type of pharmaceutical formulation chosen and the time period and interval at which such administration is carried out. In
30 some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect, provided that such larger doses are first divided into several small doses for administration
35 throughout the day.

The compounds of the invention may be administered alone or in combination with pharmaceutically acceptable

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carriers or diluents by either of the three routes previously indicated, and such administration may be carried out in single or multiple doses. More particularly, the novel therapeutic agents of this invention can be administered in a wide variety of different dosage forms, i.e., they may be combined with various pharmaceutically acceptable inert carriers in the form of tablets, capsules, lozenges, troches, hard candies, powders, sprays, creams, salves, suppositories, jellies, gels, pastes, lotions, ointments, aqueous suspensions, injectable solutions, elixirs, syrups, and the like. Such carriers include solid diluents or fillers, sterile aqueous media and various non-toxic organic solvents, etc. Moreover, oral pharmaceutical compositions can be suitably sweetened and/or flavored. In general, the therapeutically-effective compounds of this invention are present in such dosage forms at concentration levels ranging from about 5.0% to about 70% by weight.

For oral administration, tablets containing various excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine may be employed along with various disintegrants such as starch (and preferably corn, potato or tapioca starch), alginic acid and certain complex silicates, together with granulation binders like polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the active ingredient may be combined with various sweetening or flavoring agents, coloring matter or dyes, and, if so desired, emulsifying and/or suspending agents as well, together with such diluents as water,

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ethanol, propylene glycol, glycerin and various like combinations thereof.

For parenteral administration, solutions of a therapeutic compound of the present invention in either
5 sesame or peanut oil or in aqueous propylene glycol may be employed. The aqueous solutions should be suitably buffered if necessary and the liquid diluent first rendered isotonic. These aqueous solutions are suitable for intravenous injection purposes. The oily solutions are suitable for
10 intraarticular, intramuscular and subcutaneous injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques well known to those skilled in the art.

15 Additionally, it is also possible to administer the compounds of the present invention topically when treating inflammatory conditions of the skin and this may preferably be done by way of creams, jellies, gels, pastes, ointments and the like, in accordance with standard pharmaceutical
20 practice.

The activity of the compounds of the present invention as substance P antagonists may be determined by their ability to inhibit the binding of substance P at its receptor sites in bovine caudate tissue, employing
25 radioactive ligands to visualize the tachykinin receptors by means of autoradiography. The substance P antagonizing activity of the herein described compounds may be evaluated by using the standard assay procedure described by M. A. Cascieri et al., as reported in the Journal of Biological
30 Chemistry, Vol. 258, p. 5158 (1983). This method essentially involves determining the concentration of the individual compound required to reduce by 50% the amount of radiolabelled substance P ligands at their receptor sites in said isolated cow tissues, thereby affording characteristic
35 IC₅₀ values for each compound tested.

In this procedure, bovine caudate tissue is removed from a -70°C freezer and homogenized in 50 volumes (w./v.)

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of an ice-cold 50 mM Tris (i.e., trimethamine which is 2-amino-2-hydroxymethyl-1,3-propanediol) hydrochloride buffer having a pH of 7.7. The homogenate is centrifuged at 30,000 x G for a period of 20 minutes. The pellet is
5 resuspended in 50 volumes of Tris buffer, rehomogenized and then recentrifuged at 30,000 x G for another twenty- minute period. The pellet is then resuspended in 40 volumes of ice-cold 50 mM Tris buffer (pH 7.7) containing 2 mM of calcium chloride, 2 mM of magnesium chloride, 4 µg/ml of
10 bacitracin, 4µg/ml of leupeptin, 2µg of chymostatin and 200 g/ml of bovine serum albumin. This step completes the production of the tissue preparation.

The radioligand binding procedure is then carried out in the following manner, viz., by initiating the reaction
15 via the addition of 100 µl of the test compound made up to a concentration of 1 µM, followed by the addition of 100 µl of radioactive ligand made up to a final concentration 0.5 mM and then finally by the addition of 800 µl of the tissue preparation produced as described above.
20 The final volume is thus 1.0 ml, and the reaction mixture is next vortexed and incubated at room temperature (ca. 20°C) for a period of 20 minutes. The tubes are then filtered using a cell harvester, and the glass fiber filters (Whatman GF/B) are washed four times with 50 mM of Tris buffer (pH
25 7.7), with the filters having previously been presoaked for a period of two hours prior to the filtering procedure. Radioactivity is then determined in a Beta counter at 53% counting efficiency, and the IC₅₀ values are calculated by using standard statistical methods.

30 The anti-psychotic activity of the compounds of the present invention as neuroleptic agents for the control of various psychotic disorders is determined primarily by a study of their ability to suppress substance P-induced or substance P agonist induced hypermotility in guinea pigs.
35 This study is carried out by first dosing the guinea pigs with a control compound or with an appropriate test compound of the present invention, then injecting the guinea pigs

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with substance P or a substance P agonist by intracerebral administration via canula and thereafter measuring their individual locomotor response to said stimulus.

The present invention is illustrated by the following
5 examples. It will be understood, however, that the invention is not limited to the specific details of these examples.

EXAMPLE 1

1-N-Cyclohexyl-1-phenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine

10 A. α -Cyclohexylaminobenzeneacetonitrile

A solution of 0.98 g (9.4 mmol) of sodium bisulfite in 4 ml of water was treated with 0.96 ml (9.4 mmol) benzaldehyde in 5 ml of methanol. The resulting mixture was cooled to 5 - 10°C and treated with cyclohexylamine,
15 whereupon a thick precipitate was formed. With the reaction mixture still at approximately 5°C, solid potassium cyanide (0.61 g, 9.4 mmol) was added portionwise over 2 minutes. The precipitate became thick enough to halt stirring and 5 ml of 1:1 methanol water was added to facilitate stirring.
20 The reaction mixture was allowed to warm to room temperature over a 16 hour period. The mixture was then filtered and the product was washed with methanol-water and dried in air. There were obtained 1.6 grams (79.6% yield) of the above titled product. ¹H NMR (300 MHz, CDCl₃) δ 7.5 - 7.3 (m, 5H),
25 4.82 (s, 1H), 2.9 - 2.8 (m, 1H), 2.0 (d, 1H, J=12 Hz), 1.75 - 1.62 (m, 4H), 1.4 - 1.0 (m, 6H). ¹³C NMR (75 MHz, CDCl₃) δ 135.56, 128.99, 128.91, 127.29, 119.35, 54.87, 51.68, 33.87, 31.94, 25.95, 24.66, 24.27. IR CHCl₃ λ 2220 cm⁻¹. Mass Spectrum m/e 214 p+.

30 B. 1-N-Cyclohexyl-1-phenyl-1,2-ethanediamine

A solution of the above described compound from step A (200 mg, 0.94 mmol) in 5 ml of anhydrous toluene was cooled to between 20°C - 10°C. The stirred mixture was treated with 4.67 ml (5 equiv., 4.67 mmol) of diisobutylaluminum
35 hydride (Dibal-H) in toluene solution over a 5 minute period. The reaction mixture was monitored by thin layer analysis (tlc) eluting with 95:4:1 methylene chloride:

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methanol: conc. aqueous ammonium hydroxide. After 2 hours, the reaction mixture was quenched with 4.6 ml of methanol by dropwise addition to the reaction mixture at 0°C. This was followed by the careful addition of 4.6 ml of water. The reaction mixture was adjusted to pH 2 (with aqueous hydrochloric acid) and was then washed with isopropyl ether. The aqueous layer was separated and made basic to pH 12 with sodium hydroxide, after which the aqueous phase was extracted with methylene chloride. The organic layer was washed with saturated brine and dried with solid sodium sulfate. The crude material was chromatographed on silica gel using the same solvent mixture described above for tlc. There were obtained 150 mg (74%) of the desired material. ¹H NMR (300 MHz, CDCl₃) δ 7.37 - 7.22 (m, 5H), 3.76 (t, 1H, J=8.5 Hz), 2.80 (dd, 1H, J=15.4 Hz, J=8.5 Hz), 2.78 (dd, 1H, J=15 Hz, J=8.5 Hz), 2.3 (m, 1H), 1.95 (d, 1H, J=10 Hz), 1.69 (br s, 3H), 1.52 (br s, 1H), 1.12 (br s, 6H). ¹³C NMR (75 MHz, CDCl₃) δ 143.20, 128.40, 127.17, 127.03, 62.09, 53.43, 49.20, 34.79, 33.08, 26.16, 24.78. Mass Spectrum m/e 219 p⁺, 188 p-30.

C. 1-N-Cyclohexyl-1-phenyl-2-N'-[(2-methoxy-phenyl)methyl]1,2-ethanediamine

The diamine (109 mg 0.5 mmol) from step B was dissolved in 3 ml of acetic acid to which a few 3 Å molecular sieves were added. The mixture was treated with 85 mg (0.625 mmol) anisaldehyde followed by the portionwise addition of 211 mg (1.0 mmol) of sodium triacetoxyborohydride. The reaction mixture was stirred for two hours. The reaction mixture was filtered and evaporated in vacuo. The residue was taken up in 10 ml of 1 N hydrochloric acid (HCl) and extracted with ether. The aqueous phase was separated and the solution pH was adjusted to 12 with 2 M sodium hydroxide (NaOH). The aqueous phase was extracted with ether which was then washed with brine, dried with sodium sulfate and evaporated in vacuo. The residue was chromatographed on silica gel using 97:2:1 methylene chloride: methanol: conc. aqueous ammonium hydroxide as the eluant. There were obtained 70 mg (41%).

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¹H NMR (300 MHz, CDCl₃) δ 7.33 - 7.18 (m, 7H), 6.88 (t, 1H, J=7.4 Hz), 6.82 (d, 1H, J=8.0 Hz), 3.94 (dd, 1H, J=8.06 Hz, J=5.50 Hz), 3.78 (s, 2H), 3.73 (s, 3H), 2.76 - 2.64 (m, 2H), 2.31 - 2.25 (m, 1H), 2.00 - 1.53 (m, 7H), 1.10 (br s, 5H).
5 ¹³C NMR (75 MHz, CDCl₃) δ 157.61, 143.69, 129.82, 128.33, 128.13, 127.21, 126.92, 120.34, 110.14, 59.09, 56.24, 55.11, 53.56, 49.09, 34.94, 32.99, 26.24, 25.23, 24.87 ppm. IR CHCl₃ λ 1600(d), 1450 cm⁻¹. Mass spectrum m/e 339 p⁺.

The dihydrochloride salt of the title compound was prepared by dissolving 70 mg (0.2 mmol) in ether and treating the solution with an excess of hydrogen chloride (HCl) saturated ether. The salt was obtained after evaporation of the solvent and dissolution of the residue in small amount of methanol and precipitation with isopropyl ether. M.p. 222-224°C. Anal. Calc'd for C₂₂H₃₀N₂O•2HCl: C, 64.23; H, 7.84; N, 6.81%. Found: C, 63.97; H, 7.86; N, 6.73%.

EXAMPLE 2

1-N-Cyclopentyl-1-phenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-
20 ethanediamine

This compound was prepared by a procedure similar to that described in Example 1. ¹H NMR (300 MHz, CDCl₃) δ 7.34-7.17 (m, 7H), 6.88 (t, 1H, J=7.37 Hz), 6.82 (d, 1H, J=8.14 Hz), 3.80 (dd, 1H, J=8.11 Hz, J=5.57 Hz), 3.78 (s, 2H), 3.74, (s, 3H), 2.88 (quin, 1H, J=6.80 Hz), 2.77 - 2.66 (m, 2H), 1.95 (br s, 1H), 1.80 - 1.20 (m, 8H). ¹³C NMR (75 MHz, CDCl₃) δ 157.5, 143.16, 129.86, 128.34, 128.20, 127.35, 127.05, 120.35, 110.14, 61.07, 57.14, 55.88, 55.11, 49.12, 34.03, 32.60, 23.82, 23.78. IR CHCl₃ λ 1605(d), 1450 cm⁻¹.
25 Mass spectrum m/e 325 p⁺. High Resolution Mass Spectrum (HRMS) calc'd for C₂₁H₂₉N₂O (p+1): 325.2273. Found: 325.2250.

The dihydrochloride salt of the title compound was prepared as described in Example 1C. M.p. = 223 - 224°C. Anal Calc'd for C₂₁H₂₈N₂O•2HCl: C, 63.47; H, 7.61; N, 7.05%.
35 Found: C, 63.46; H, 7.61; N, 7.02%.

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EXAMPLE 31-N-Propyl-1-phenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine

The title compound as prepared by a procedure similar to that described in Example 1. ¹H NMR (300 MHz, CDCl₃) δ 7.34-7.18 (m, 7H), 6.89 (dt, 1H, 7.39 Hz, J=1.04 Hz), 6.83 (d, 1H, J=8.10 Hz), 3.79 (m, 2H), 3.75 (s, 3H), 3.74-3.70 (m, 1H), 2.80-2.67 (m, 2H), 2.43-2.38 (m, 2H), 1.52-1.40 (m, 2H), 0.893-0.844 (t, 3H, J=7.37 Hz). ¹³C NMR (75 MHz, CDCl₃) δ 157.62, 143.07, 129.82, 128.36, 128.17, 127.30, 127.05, 120.35, 110.17, 62.88, 55.88, 55.13, 49.69, 49.21, 29.72, 23.42, 11.85 ppm. IR CHCl₃ λ 1600(d), 1450 cm⁻¹. Mass spectrum m/e 229 p⁺.

EXAMPLE 4

15 1-(R,S)-2-(R,S)-1-Amino-1-phenyl-2-[(2-methoxy)-phenylmethylamino]propane

A. 1-(R,S)-2-(R,S)-1-N-Phthalimido-1-phenyl-2-nitropropane

A solution of phthalimide (20.0 g, 135.93 mmol) in 400 ml of ethanol was treated with 9.87 g (149.53 mmol) of potassium hydroxide and stirred for 15 minutes. The mixture was treated with 28.80 g (176.71 mmol) of 1-phenyl-2-nitropropene and the reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was quenched with 72.71 g (1.35 mol) of solid ammonium chloride and then diluted with 100 ml of ethyl acetate and 1500 ml of water. The aqueous layer was extracted (6 x 300 ml) with ethyl acetate. The combined organic layers were dried with magnesium sulfate and evaporated. The residue (yellow paste) was treated with 250 ml of isopropyl ether and stirred for 5 minutes. The solids were filtered and washed with 50 ml isopropyl ether and then 3 x 60 ml of ethanol followed by air drying. There were obtained 18.35 g of a mixture containing the desired material as a single isomer contaminated only by phthalimide. The crude material was used directly in the next step.

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B. 1-(R,S)-2-(R,S)-1-N-Phthalimido-1-phenyl-2-aminopropane

A mixture of 125 g Raney nickel (prewashed with water until the aqueous supernatant was neutral (pH 7)) was charged into a 500 ml Parr bottle which was flushed with nitrogen. To the system were added 20 ml of methanol followed by 9.0 g of the crude product from the previous step and the mixture was diluted with 200 ml of methanol. The mixture was placed under a hydrogen atmosphere at 45 psi for 12 hours. Thin layer analysis (tlc) (5% methanol in methylene chloride) indicated that starting material had been consumed. The catalyst was removed by filtration through Celite® and the filtrate was evaporated in vacuo. The residue was treated with 100 ml of methylene chloride whereupon residual phthalimide precipitated. The mixture was filtered once again and the filtrate was evaporated in vacuo. The residue was chromatographed on silica gel eluting with 2% methanol in methylene chloride. There were obtained 2.65 g (%) of the title compound as a single isomer. ¹H NMR (250 MHz, CDCl₃) δ 7.83-7.80 (2H, m), 7.72-7.67 (2H, m), 7.60-7.56 (2H, m), 7.37-7.28 (3H, m), 4.90-4.86 (1H, d, J=10.6 Hz), 4.41-4.29 (1H, dq, J=10.6 Hz, J=6.4 Hz), 1.44 (2H, br s), 1.10-1.06 (3H, d, J=6.4 Hz).

C. 1-(R,S)-2-(R,S)-1-N-Phthalimido-1-phenyl-2-[(2-methoxy)phenyl-methylamino]propane

A solution of 2.18 g (7.77 mmol) of the product from step B in 75 ml of toluene was treated with 1.06 g (7.77 mmol) of 2-methoxybenzaldehyde. The resulting reaction mixture was heated to reflux over a Dean-Stark water separator for 16 hours. The reaction was then cooled to room temperature and was evaporated in vacuo to afford 3.10 g of an imine as a yellow solid which was used without purification. ¹H NMR (250 MHz, CDCl₃) δ 8.77 (s, 1H), 7.73-7.69 (m, 5H), 7.59-7.54 (m, 2H), 7.39-7.23 (m, 5H), 6.84-6.77 (m, 2H), 5.50 (d, 1H, J=10.7 Hz), 4.93-4.83 (dq, 1H, J=10.7 Hz, J=6.4 Hz), 3.76 (s, 3H), 1.20-1.17 (d, 3H, J=6.4 Hz). A solution of the above described imine (3.07 g, 7.70

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mmol) was taken up in 70 ml of dichloroethane was treated with 1.64 g (7.70 mmol) of sodium triacetoxyborohydride. The reaction mixture was stirred for 1.5 hours and was monitored by thin layer analysis (1% methanol in methylenechloride). At this point, 1.64 g of sodium triacetoxyborohydride were added and stirring was continued for an additional 16 hours. The reaction mixture was quenched with 300 ml of saturated aqueous bicarbonate and the mixture was extracted with 2 volumes of dichloroethane. The combined organic layers were washed with aqueous brine solution and dried with magnesium sulfate. The residue was chromatographed on silica gel using 20% ethyl acetate in hexane as eluent to provide 2.59 g (84%) of an oil. ¹H NMR (250 MHz, CDCl₃) δ 7.81-7.78 (m, 2H), 7.71-7.66 (m, 2H), 7.61-7.58 (m, 2H), 7.35-7.25 (m, 4H), 7.21-7.13 (m, 2H), 6.84-6.78 (dt, 1H, J=7.37 Hz, J=1.0 Hz), 6.74-6.71 (d, 1H, J=8.17 Hz), 5.30 (s, 1H), 5.09-5.05 (d, 1H, 10.96 Hz), 4.22-4.15 (dq, 1H, J=10.96 Hz, J=6.36 Hz), 3.90-3.68 (dd, 2H, J=13.0 Hz), 3.54 (s, 3H), 1.05-1.03 (d, 3H, J=6.36 Hz).

D. 1-(R,S)-2-(R,S)-1-Amino-1-phenyl-2-[(2-methoxy)-phenylmethylamino] propane

A solution of 2.38 g (5.94 mmol) of 1-N-phthalimido-1-phenyl-2-[(2-methoxy)phenylmethylamino]propane, prepared by the procedure of step C, in 85 ml of ethanol was treated with 281 μl (5.94 mmol) hydrazine hydrate and the reaction mixture was heated to reflux. After 2.5 hours, the mixture was allowed to cool to room temperature and was stirred overnight. The reaction mixture was treated with 1.48 ml (17.83 mmol) of concentrated hydrochloric acid. The resulting suspension was filtered and the filtrate was diluted with water (200 ml) and was washed with ether (5x100 ml). The aqueous layer was adjusted to pH 12 with 25% NaOH solution and the basic phase was extracted with ethyl acetate (3x100 ml). The organic layer was dried over sodium sulfate and stripped to an oil. There was obtained 1.18 g (73% yield). ¹H NMR (250 MHz, CDCl₃) δ 7.36-7.22 (m, 7H), 6.95-6.83 (m, 2H), 3.95 & 3.72 (dd, 2H, J=13.3 Hz), 3.77 (s,

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3H), 3.73 [d(obsc), 1H], 2.79-2.73 (dq, 1H, J=6.38 Hz, J=7.55 Hz), 2.01 (br s, 3H), 0.99-0.96 (d, 3H, J=6.38 Hz). ¹³C NMR (75.47 MHz, CDCl₃) δ 157.64, 144.67, 129.88, 128.39, 128.32, 127.97, 127.02, 120.46, 110.20, 61.33, 58.26, 55.19, 46.80, 17.15 ppm. IR (CHCl₃) λ 1601, 1487, 1461 cm⁻¹. High Resolution Mass Spectrum (HRMS) calc'd for C₁₇H₂₂N₂O (p+1): 271.18103. Found: 271.1802.

The dihydrochloride was prepared by treating a solution of the above prepared diamine in ether with a saturated solution of hydrogen chloride in ether. The mixture was evaporated and the residue was taken up in methanol, filtered through glass wool and recrystallized from methanol/ether. M.p. 244-245°C. Anal. calc'd for C, 59.48; H, 7.05; N, 8.16. Found: C, 59.31; H, 7.01; N, 8.00.

15

EXAMPLE 5

(1R*, 2S*)-1-Cyclohexylamino-1-phenyl-2-[(2-methoxy)-phenylmethylamino]propane

A. (1R, 2S)-1-Hydroxy-1-phenyl-2-[(2-methoxy)-phenyl-methylamino]propane

20 A solution of 1.00 g (6.61 mmol) (1R, 2S)-(-)-norepinephrine and 1.12 g (8.26 mmol) of o-anisaldehyde in 20 ml of acetic acid was treated with 1.5 g of 3 Å molecular sieves. The mixture was treated with 2.8 g (13.22 mmol) of sodium triacetoxyborohydride in 0.1 g increments over 20 minutes.

25 The reaction mixture was stirred at room temperature for 18 hours under a nitrogen atmosphere. The reaction was judged to be complete by thin layer analysis (eluting with 9:1 methylene chloride:methanol), the mixture was filtered and the filtrate was evaporated in vacuo. The residue was taken

30 up in 25 ml of water and the mixture was treated with 1N HCl until the solution pH was approximately 3. The aqueous phase was extracted twice with ether (25 ml) and was then treated with 2N NaOH until pH 12 was reached. The aqueous layer was again extracted with ether (3 x 50 ml). The

35 organic layer was dried with magnesium sulfate and was evaporated to dryness. There were obtained 1.11 g (62% yield) of a white solid after chromatography (eluting with

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95% ethyl acetate/5% triethyl amine) on silica gel. M.P. 84-86°C. ¹H NMR (CDCl₃, 300 MHz) δ 7.39-7.21 (7 H, m), 7.0-6.92 (1H, t, J=8.5 Hz), 6.91-6.88 (1H, d, J=8.0 Hz), 4.82 (d, 1H, J=4.0 Hz), 3.90 (s, 2H), 3.82 (s, 3H), 2.97-2.88 (dq, 1H, J=7 Hz, J=4.0 Hz), 0.82 (d, 3H, J=7 Hz) ppm. ¹³C NMR (DEPT, CDCl₃, 75.47 MHz) δ 157.74 (s), 141.65 (s), 129.86 (d), 128.50 (d), 128.14 (s), 128.05 (d), 126.93 (d), 126.12 (d), 120.49 (d), 110.36 (d), 72.83 (d), 57.25 (d), 55.23 (q), 46.68 (t), 14.77 (q) ppm. IR (KBr) λ 3500 - 2400 (br), 1600, 1480, 1460, 1240, 1050, 1030 cm⁻¹. HRMS calc'd for C₁₇H₂₁NO₂: 271.1567. Found 271.1603.

B. (1R,S,2S)-1-Chloro-1-phenyl-2-[(2-methoxyphenyl)methylamino]propane

A solution of the hydrochloride salt of the title compound of Example 5A was prepared by addition of 2.1 g (6.82 mmol) of (1R, 2S)-1-hydroxy-1-phenyl-2-[(2-methoxy)phenylmethylamino]propane to a saturated solution of hydrogen chloride (HCl) gas in methylene chloride followed by evaporation in vacuo. The residue was dissolved in 0.75 ml (10.23 mmol) of thionyl chloride and the mixture was heated to reflux. After a period of 40 minutes, the reaction mixture was evaporated in vacuo to yield the product as a mixture of two diastereomers (2.8:1 ratio by ¹H NMR) and as a yellow solid which was used directly in part D.

C. (1R,S,2S)-1-Chloro-1-phenyl-2-[(2-methoxyphenyl)methylamino]propane

A solution of the hydrochloride salt of the title compound of example 5A was prepared by addition of 1.0 g (3.69 mmol) of (1R, 2S)-1-hydroxy-1-phenyl-2-[(2-methoxy)phenylmethylamino]-propane to a saturated solution of HCl (g) in methylene chloride followed by evaporation in vacuo. The residue was dissolved in 10 ml of chloroform and chilled to 5°C. To the solution 0.66 gm (5.53 mmol) of thionyl chloride in 10 ml of chloroform was added slowly via syringe and the mixture was allowed to warm to room temperature. After a period of 40 minutes

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the reaction mixture was evaporated in vacuo to yield the product as a mixture of two diastereomers (44%:55% ratio by ¹H NMR) and as a yellow solid which was used directly in part D.

5 D. (1R*,2S*)-1-Cyclohexylamino-1-phenyl-2-[(2-methoxy)phenylmethylamino]propane

A solution of the previously prepared (1R,S,2S)-1-chloro-1-phenyl-2-[(2-methoxy)phenyl-methylamino]propane in ethanol [1.0 g (3.06 mmol) in 5 ml] was treated with 1.05 ml
10 (9.19 mmol) cyclohexylamine and the reaction mixture was heated to reflux for 50 minutes. The reaction mixture was allowed to cool to room temperature and was then filtered to remove a small amount of a white precipitate. The filtrate was evaporated in vacuo and the residue was chromatographed
15 on silica gel eluting with hexane:ethyl acetate (7:3). The minor, more polar material was collected (80 mg) and was dissolved in ether and treated with a saturated solution of HCl (g) in ether. The resulting gummy solid was collected and repulped in petroleum ether to afford 90 mg of the
20 dihydrochloride salt as a light tan solid. M.p. 173 - 181°C (decomp.). ¹H NMR free base (CDCl₃, 300 MHz) δ 7.32-7.14 (m, 7H), 6.88 (t, 1H, J=7 Hz), 6.78 (d, 1H, J=7 Hz), 3.78 (dd, 2H, J=13 Hz), 3.82 [d(obsq), 1H], 3.7 (s, 3H), 2.76 (quin, 1H, J=6 Hz), 2.24-2.12 (m, 1H), 2.0-1.46 (m, 7 H), 1.19-1.0
25 (m, 4H), 0.98 (d, 3H, J=6 Hz) ppm. ¹³C NMR (CDCl₃, 75.47 MHz) δ 157.67, 142.84, 129.85, 128.53, 128.15, 128.08, 128.02, 126.63, 120.30, 110.09, 62.58, 56.97, 55.05, 53.63, 46.82, 34.97, 32.96, 26.30, 25.29, 24.91, 16.2, 14.24 ppm. IR (CHCl₃) λ 1600, 1450 cm⁻¹. HRMS C₂₃H₃₂N₂O (no p⁺ found). Calc'd for C₁₀H₁₄NO: 164.1075. Found: 164.1066. Calc'd for C₁₃H₁₈N:
30 188.1439. Found: 188.1441.

The title compounds of Examples 6-19 were prepared by a method analogous to that described in Example 1.

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EXAMPLE 6

1-N-cyclohexyl-1-phenyl-2-N'-[(2-methoxy-5-trifluoromethoxyphenyl)methyl]-1,2-ethanediamine

HRMS m/e Calc'd for $C_{23}H_{29}N_2O_2F_3$: 422.2174. Found
5 422.21356.

EXAMPLE 7

1-N-pyrrolidyl-1-phenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine dihydrochloride

Calc'd for $C_{20}H_{26}N_2O \cdot 2HCl$: C: 62.66, H: 7.36, N: 7.31.
10 Found C: 62.26, H: 7.38, N: 7.33.

EXAMPLE 8

1-N-methyl-1-phenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine dihydrochloride

Calc'd for $C_{17}H_{22}N_2O \cdot 2HCl$: C: 59.48, H: 7.05, N: 8.16.
15 Found C: 59.39, H: 7.25, N: 8.02.

EXAMPLE 9

1-N-phenylmethyl-1-phenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine dihydrochloride

Calc'd for $C_{23}H_{26}N_2O \cdot 2HCl$: C: 65.87, H: 6.73, N: 6.68.
20 Found C: 65.63, H: 6.77, N: 6.64.

EXAMPLE 10

1-N-cyclooctyl-1-phenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine dihydrochloride

Calc'd for $C_{24}H_{34}N_2O \cdot 2HCl$: C: 65.59, H: 8.26, N: 6.37.
25 Found C: 65.60, H: 8.19, N: 6.20.

EXAMPLE 11

1-N-phenyl-1-phenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine dihydrochloride

Calc'd for $C_{22}H_{24}N_2O \cdot 1HCl$: C: 71.63, H: 6.83, N: 7.59.
30 Found C: 71.26, H: 6.83, N: 7.65.

EXAMPLE 12

1-N-phenyl-1-phenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine dihydrochloride

Calc'd for $C_{20}H_{26}N_2O \cdot 2HCl$: C: 62.66, H: 7.36, N: 7.31.
35 Found C: 62.26, H: 7.48, N: 7.24.

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EXAMPLE 13

1-N-(2-adamantyl)-1-phenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine dihydrochloride

Calc'd for $C_{26}H_{34}N_2O \cdot 2HCl$: C: 67.38, H: 7.83, N: 6.04.

5 Found C: 67.23, H: 8.04, N: 6.10.

EXAMPLE 14

1-N-(1,1-dimethylethyl)-1-phenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine dihydrochloride

2-HCl Salt mp = 155-157°C.

10

EXAMPLE 15

1-N-cyclopropyl-1-phenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine dihydrochloride

2-HCl Salt mp = 140-141°C.

EXAMPLE 16

15 1-N-isopropyl-1-phenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine dihydrochloride

Calc'd for $C_{19}H_{26}N_2O \cdot 2HCl$: C: 61.45, H: 7.60, N: 7.54.

Found C: 61.19, H: 7.67, N: 7.52.

EXAMPLE 17

20 1-N-(1-phenylethyl)-1-phenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine dihydrochloride

2-HCl Salt mp - 226-228°C.

EXAMPLE 18

25 1-N-(2-norbornyl)-1-phenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine dihydrochloride

Calc'd for $C_{23}H_{30}N_2O \cdot 2HCl$: C: 65.24, H: 7.62, N: 6.62.

Found C: 65.48, H: 7.95, N: 6.65.

EXAMPLE 19

30 1-N-(2-aza-bicyclo[4.4.0]decane)-1-phenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine dihydrochloride

HRMS m/e Calc'd for $C_{25}H_{34}N_2O$: 378.2663. Found 378.2702.

EXAMPLE 20

1,1-Diphenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine

35

A. α,α -Diphenyl- α -aminoacetonitrile

A solution of 4.05 ml (0.03 mol) of trimethylsilylcyanide in 20 ml of dry benzene was treated

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with 0.44 gm (0.001 mol) zinc iodide and 4.63 ml (0.028 mol) of benzophenoneimine. The reaction mixture was stirred at room temperature for 10 min., whereupon a white precipitate formed. The reaction mixture was quenched with wet ether and stirred for 2 hours. The liquid phase was washed with saturated brine solution and dried over sodium sulfate and evaporated in vacuo. The residue was recrystallized from ether-hexane to afford 2.4 gm (38%). ¹H NMR (CDCl₃, 300 MHz) δ 7.7-7.6 (m, 4H), 7.4-7.28 (m, 6H); ¹³C NMR (CDCl₃, 75.5 MHz) δ 141.2, 128.9, 128.6, 125.8, 123.4, 60.8.

B. 1,1-Diphenyl-1,2-ethanediamine

α,α-Diphenyl-α-aminoacetonitrile (1.0 gm, 0.0048 mol) was dissolved in 6 ml of toluene and was cooled to -20°C. The solution was treated with 19.2 ml (0.0192 mol) of 1 M diisobutylaluminum hydride (DiBal-H) and stirred at -20°C for 3 hours. The reaction mixture was quenched with 2.0 ml of methanol followed by 50 ml of water. The reaction mixture was acidified to pH 1.0 and the aqueous phase was extracted with ether several times. The remaining aqueous phase was basified to pH 13 with 2N sodium hydroxide solution and extracted with methylene chloride. The organic phase was dried and evaporated to afford 0.946 g (92%) of the desired material as an oil.

¹H NMR (CDCl₃, 300 MHz) δ 7.38-7.15 (m, 10H), 3.35 (s, 2H); ¹³C NMR (CDCl₃, 75.5 MHz) δ 147.0, 128.3, 126.8, 126.6, 62.1, 52.4.

C. 1,1-Diphenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine

1,1-Diphenyl-1,2-ethanediamine (25 mg, 0.118 mmol) prepared in the previous step was dissolved in 2 ml of acetic acid and treated with 44 mg 3 Å molecular sieves. The stirred mixture was treated with 20 mg (0.147 mmol) o-anisaldehyde followed by portionwise addition of 25 mg (0.118 mmol) sodium triacetoxyborohydride. The reaction mixture was stirred for 2 hours and was then diluted with 20 ml of water, acidified to pH 1 with aqueous 2N HCl aq and extracted with ether. The aqueous phase was basified with

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aqueous sodium bicarbonate and extracted with methylene chloride. The organic phase was washed with brine and then dried and evaporated. The residue was chromatographed on silica eluting with 96:3:1 CH₂Cl₂:MeOH:NH₄OH. There was
5 obtained 39 mg (68%) of the title material. ¹H NMR (CDCl₃, 300 MHz) δ 7.38-7.12 (m, 12H), 6.90 (t, 1H, J=7 Hz), 6.8 (d, 1H, J=8 Hz), 3.8 (s, 2H), 3.65 (s, 3H), 3.25 (s, 2H); ¹³C NMR (CDCl₃, 75.5 MHz) δ 157.6, 147.2, 129.7, 128.3, 128.1, 126.7, 126.5, 120.3, 110.1, 61.1, 59.6, 55.0, 49.9;

10 HRMS calc'd for C₂₂N₂₄N₂O 332.1883; found 332.18684.

The title compounds of Examples 20A-22 were prepared by a procedure analogous to that described in Example 20.

EXAMPLE 20A

1,1-diphenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-
15 ethanediamine dihydrochloride

Calc'd for C₂₂H₂₄N₂O•2HCl•0.5 H₂O: C: 63.77, H: 6.57, N: 6.76. Found C: 64.03, H: 6.72, N: 6.78

EXAMPLE 21

1,1-diphenyl-2-N'-[(2,5-dimethoxyphenyl)methyl]-1,2-
20 ethanediamine

HRMS m/e Calc'd for C₂₃H₃₄N₂O: 363.2066. Found 363.20730.

EXAMPLE 22

1,1-diphenyl-2-N'-[(2,4-dimethoxyphenyl)methyl]-1,2-
25 ethanediamine dihydrochloride

Calc'd for C₂₃H₂₆N₂O₂•2HCl: C: 63.45, H: 6.48, N: 6.43. Found C: 63.07, H: 6.36, N: 6.31.

The title compounds of Examples 23-28 were prepared by a method analogous to that described in Example 1.

30 EXAMPLE 23

1-N-cyclohexyl-1-N-(6-n-hexanol)-1-phenyl-2-N'-[(2-
methoxyphenyl)methyl]-1,2-ethanediamine

ms m/e 439 (p+1)

EXAMPLE 24

35 1-N-cyclohexyl-1-N-(3-phenylpropyl)-1-phenyl-2-N'-[(2-
methoxyphenyl)methyl]-1,2-ethanediamine

ms m/e 457 (p+1)

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EXAMPLE 25

3,3-diphenyl-2-N-cyclopentyl-1-N'-[(2-methoxyphenyl)methyl]-1,2-propanediamine dihydrochloride

Calc'd for $C_{28}H_{34}N_2O \cdot 2HCl$: C: 68.98, H: 7.44, N: 5.75.

5 Found C: 68.69, H: 7.79, N: 5.47.

EXAMPLE 26

1-N-(2-phenylethyl)-1-(3,4-methylenedioxyphenyl)-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine dihydrochloride

Calc'd for $C_{25}H_{28}N_2O_3 \cdot 2HCl$: C: 62.89, H: 6.33, N: 5.87.

10 Found C: 62.90, H: 6.09, N: 5.82.

EXAMPLE 27

1-N-cyclopentyl-1-(2-naphthyl)-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine dihydrochloride

Calc'd for $C_{25}H_{30}N_2O \cdot 2HCl$: C: 67.11, H: 7.21, N: 6.26.

15 Found C: 66.75, H: 7.12, N: 6.07.

EXAMPLE 28

1-N-cyclohexyl-1-cyclohexyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine dihydrochloride

Calc'd for $C_{22}H_{36}N_2O \cdot 2HCl$: C: 63.30, H: 9.18, N: 6.71.

20 Found C: 63.31, H: 9.58, N: 6.72.

The title compounds of Examples 29-34 were prepared by a procedure analogous to that described in Example 4:

EXAMPLE 29

(1R,S)-cycloheptylamino-1-phenyl-(2R,S)-[(2-methoxyphenyl)methylamino]propane

25 HRMS m/e Calc'd for $C_{24}H_{35}N_2O$ (FAB, p+1) 367.27492. Found 367.2752.

EXAMPLE 30

(1R,S)-amino-1-phenyl-(2R,S)-[(2-methoxyphenyl)methylamino]propane

30 HRMS m/e Calc'd for $C_{17}H_{23}N_2O$ (FAB, p+1) 271.18103. Found 271.1802.

EXAMPLE 31

(1R,S)-(4-pyranylamino-1-phenyl-(2R,S)-[(2-methoxyphenyl)methylamino]propane

35 HRMS m/e Calc'd for $C_{22}H_{31}N_2O_2$ (FAB, p+1) 355.23854. Found 355.2391.

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EXAMPLE 32

(1R,S)-cyclohexylamino-1-phenyl-(2R,S)-[(2-methoxyphenyl)methylamino]propane

Ms m/e (FAB) 353 (p+1).

5

EXAMPLE 33

(1R,S)-cyclopentylamino-1-phenyl-(2R,S)-[(2-methoxyphenyl)methylamino]propane dihydrochloride

Calc'd for $C_{22}H_{30}N_2O \cdot 2HCl$: C: 64.23, H: 7.84, N: 6.81.

Found C: 63.83, H: 7.76, N: 6.71.

10

EXAMPLE 34

(1R,S)-n-propylamino-1-phenyl-(2R,S)-[(2-methoxyphenyl)methylamino]propane

Ms m/e (FAB) 313 (p+1).

The title compounds of Examples 35-42 were prepared by
a method analogous to that described in Example 5.

15

EXAMPLE 35

(1R,S)-cyclohexylamino-1-phenyl-(2S,R)-[(2-methoxyphenyl)methylamino]propane dihydrochloride

Calc'd for $C_{22}H_{32}N_2O \cdot 2HCl \cdot 0.5 H_2O$: C: 63.59, H: 8.12, N:

20 6.45. Found C: 63.29, H: 8.27, N: 6.24.

EXAMPLE 36

(1R,S)-N-pyrrolidyl-1-phenyl-(2S,R)-[(2-methoxyphenyl)methylamino]propane dihydrochloride

Calc'd for $C_{21}H_{28}N_2O \cdot 2HCl \cdot 0.5 H_2O$: C: 62.07, H: 7.69, N:

25 6.89. Found C: 62.11, H: 7.82, N: 6.96.

EXAMPLE 37

(1R,S)-N-piperidyl-1-phenyl-(2S,R)-[(2-methoxyphenyl)methylamino]propane

HRMS m/e Calc'd for $C_{22}H_{31}N_2O$ (p+1): 339.2429. Found

30 339.2393.

EXAMPLE 38

(1R,S)-cyclopentylamino-1-phenyl-(2S,R)-[(2-methoxyphenyl)methylamino]propane

HRMS m/e Calc'd for $C_{22}H_{31}N_2O$ (p+1): 339.2429. Found

35 339.2421.

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EXAMPLE 39

(1R,S)-cyclooctylamino-1-phenyl-(2S,R)-[(2-methoxyphenyl)methylamino]propane dihydrochloride

Calc'd for $C_{25}H_{36}N_2O \cdot 2HCl$: C: 66.21, H: 8.45, N: 6.18.

5 Found C: 65.88, H: 8.78, N: 5.98.

EXAMPLE 40

(1R,S)-propylamino-1-phenyl-(2S,R)-[(2-methoxyphenyl)methylamino]propane

HRMS m/e Calc'd for $C_{20}H_{28}N_2O$: 312.2195. Found 312.2169.

10

EXAMPLE 41

(1R,S)-methylamino-1-phenyl-(2S,R)-[(2-methoxyphenyl)methylamino]-3-methoxypropane

HRMS m/e Calc'd for $C_{19}H_{26}N_2O_2$: 314.1918. Found 314.1718.

15

EXAMPLE 42

(1R,S)-amino-1-phenyl-(2S,R)-[(2-methoxyphenyl)methylamino]-3-methoxypropane

Ms m/e (FAB) 301 (p+).

The title compounds of Examples 43 to 46 were prepared
20 by a method analogous to that described in Example 1.

EXAMPLE 43

1-N-cyclohexyl-1-phenyl-2-N'-[(2-methoxy-5-tert-butylphenyl)methyl]-1,2-ethanediamine

1H NMR ($CDCl_3$, 250 MHz) δ 7.35-7.22 (m, 7H), 6.78 (br.d, 1H, $J=10.7Hz$), 3.99 (dd, 1H, $J=7.9Hz$, $J=6.4Hz$), 3.79 (s, 2H), 3.72 (s, 3H), 2.75 (m, 2H), 2.31 (m, 1H), 2.02-1.51 (m, 7H), 1.30 (s, 9H), 1.25-1.0 (m, 3H) ppm.

^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 155.42, 143.55, 142.98, 128.34, 127.20, 127.00, 126.94, 124.62, 109.67, 58.93, 56.15, 55.17, 53.54, 49.38, 34.91, 34.04, 32.94, 31.55, 26.21, 25.17, 24.82 ppm.

IR (neat) λ 3300 (w), 2940, 1610 (w), 1510, 1460, 1375, 1250 cm^{-1} .

Mass spectrum m/e 394 (p+).

35

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EXAMPLE 441-N-cyclohexyl-1-phenyl-2-N'-[(2-methoxy-5-isopropyl-phenyl)methyl]-1,2-ethanediamine

¹H NMR (CDCl₃, 300 MHz) δ 7.35-7.20 (m, 6H), 7.06 (br.s, 1H), 6.77 (d, 1H, J=8.6Hz), 3.96 (dd, 1H, J=8.0Hz, J=5.6Hz), 3.75 (s, 2H), 3.71 (s, 3H), 2.90-2.65 (m, 3H), 2.30 (m, 1H), 2.02-1.49 (m, 7H), 1.22 (d, 6H, J=6.9Hz), 1.25-0.95 (m, 5H) ppm.

¹³C NMR (CDCl₃, 75.47 MHz) δ 155.74, 143.64, 140.70, 128.33, 128.02, 127.21, 126.93, 125.58, 110.03, 58.99, 56.24, 55.21, 53.55, 49.24, 34.92, 33.28, 32.96, 26.22, 25.19, 24.83, 24.24, 24.22 ppm.

IR (neat) λ 3300 (w), 2930, 1610 (w), 1510, 1455, 1250 cm⁻¹.

Mass spectrum m/e 380 (p+).

EXAMPLE 451-N-cyclohexyl-1-phenyl-2-N'-[(2-methoxy-4,5-dimethyl-phenyl)methyl]-1,2-ethanediamine

¹H NMR (CDCl₃, 300 MHz) δ 7.34-7.20 (m, 5H), 6.93 (s, 1H), 6.62 (s, 1H), 3.94 (dd, 1H, J=8.1Hz, J=5.4Hz), 3.71 (s, 3H), 3.71 (s.obsc, 2H), 2.73 (dd, 1H, J=11.7Hz, J=5.4Hz), 2.66 (dd, 1H, J=11.7Hz, J=8.1Hz), 2.30 (m, 1H), 2.23 (s, 3H), 2.17 (s, 3H), 2.0-1.5 (m, 7H), 1.07 (m, 5H) ppm.

¹³C NMR (CDCl₃, 75.47 MHz) δ 155.65, 143.79, 135.99, 131.31, 128.30, 127.85, 127.25, 126.87, 125.51, 112.02, 59.10, 56.27, 55.29, 53.57, 48.77, 34.95, 32.97, 26.25, 25.23, 24.88, 19.93, 18.70 ppm.

IR (neat) λ 3300 (w), 2910, 2840, 1610 (w), 1500, 1450 (sh), 1250, 1200 cm⁻¹.

Mass spectrum m/e 367 (p+).

EXAMPLE 461-N-cyclohexyl-1-N-(6-hydroxyhexyl)-1-phenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine

¹H NMR (CDCl₃, 250 MHz) δ 7.30-7.17 (m, 7H), 6.92 (t, 1H, J=7.4Hz), 6.84 (d, 1H, J=8.4Hz), 3.99 (dd, 1H, J=8.8Hz, J=5.7Hz), 3.87 (d, 1H, J=13.3Hz), 3.76 (s, 3H), 3.75 (d, 1H, J=13.3Hz), 3.56 (t, 2H, J=6.5Hz), 3.10 (dd, 1H, J=11.2Hz,

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J=9.1Hz), 2.75 (dd, 1H, J=11.3Hz, J=5.7Hz), 2.60-2.25 (m, 5H), 1.75-0.88 (br.m, 18H) ppm.

¹³C NMR (CDCl₃, 62.90 MHz) δ 157.5, 141.5, 129.9, 128.2, 128.1, 127.9, 126.8, 120.2, 110.0, 62.4, 56.8, 54.9, 50.6, 5 49.2, 45.9, 33.0, 32.8, 30.4, 29.8, 27.0, 26.6, 26.2, 26.1, 25.6 ppm.

IR (neat) λ 3000 (w), 2940, 2870, 1620 (w), 1500 (w), 1460, 1200 (br), 1040 (br) cm⁻¹.

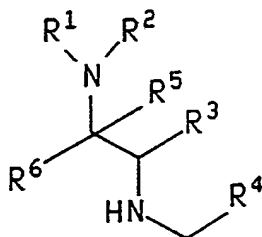
Mass spectrum (dihydrochloride salt) FAB 4397 (p⁺).

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CLAIMS

1. A compound of the formula

5

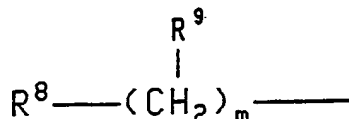


I

- 10 wherein R¹ is hydrogen, (C₁-C₈) alkyl, a saturated (C₆-C₁₀) carbocyclic ring system containing two fused rings, a saturated (C₆-C₁₀) carbocyclic bridged ring system containing two rings, or benzyl wherein the phenyl moiety of said
 15 substituents independently selected from halo, (C₁-C₆) alkyl optionally substituted with from one to three fluorine atoms and (C₁-C₈) alkoxy optionally substituted with from one to three fluorine atoms;

R² is hydrogen, benzyl or a group of the formula

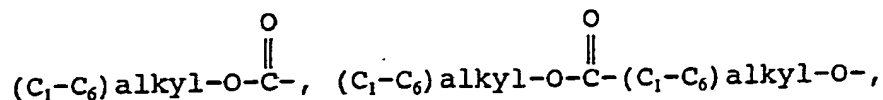
20



- 25 wherein m is an integer from zero to twelve, and any one of the carbon-carbon single bonds of (CH₂)_m, wherein both carbon atoms of such bond are bonded to each other and to another carbon atom of the (CH₂)_m chain, may optionally be replaced by a carbon-carbon double or triple bond, and any one of the
 30 carbon atoms of (CH₂)_m may optionally be substituted with R⁹;

R⁸ and R⁹ are independently selected from hydrogen, hydroxy, halo, amino, carboxy, carboxy(C₁-C₆)alkyl, (C₁-C₆)alkylamino, di-(C₁-C₆)alkylamino, (C₁-C₆)alkoxy,

35



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5 $(C_1-C_6)alkyl-\overset{\overset{O}{\parallel}}{C}-O-$, $(C_1-C_6)alkyl-\overset{\overset{O}{\parallel}}{C}-(C_1-C_6)alkyl-O-$,
 $(C_1-C_6)alkyl-\overset{\overset{O}{\parallel}}{C}-$, (C_1-C_6) straight or branched alkyl, (C_3-C_7)
 10 cycloalkyl wherein one of the carbon atoms may optionally be
 replaced by nitrogen, oxygen or sulfur; aryl selected from
 phenyl and naphthyl; heteroaryl selected from indanyl,
 thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl,
 isoxazolyl, triazolyl, tetrazolyl and quinolyl; phenyl- $(C_2-$
 15 $C_6)alkyl$, benzhydryl and benzyl, wherein each of said aryl
 and heteroaryl groups and the phenyl moieties of said
 benzyl, phenyl- $(C_2-C_6)alkyl$ and benzhydryl may optionally be
 substituted with one or two substituents independently
 selected from halo, nitro, $(C_1-C_6)alkyl$ optionally
 20 substituted with from one to three fluorine atoms, $(C_1-$
 $C_6)alkoxy$ optionally substituted with from one to three
 fluorine atoms,
 25 trifluoromethyl, amino, $(C_1-C_6)-alkylamino$, $(C_1-C_6)alkyl-O-\overset{\overset{O}{\parallel}}{C}-$,
 $(C_1-C_6)alkyl-O-\overset{\overset{O}{\parallel}}{C}-(C_1-C_6)alkyl-$, $(C_1-C_6)alkyl-\overset{\overset{O}{\parallel}}{C}-O-$,
 30 $(C_1-C_6)alkyl-\overset{\overset{O}{\parallel}}{C}-(C_1-C_6)alkyl-O-$, $(C_1-C_6)alkyl-\overset{\overset{O}{\parallel}}{C}-$,
 $(C_1-C_6)alkyl-\overset{\overset{O}{\parallel}}{C}-(C_1-C_6)alkyl-$, di- $(C_1-C_6)alkylamino$,
 35 $-\overset{\overset{O}{\parallel}}{C}NH-(C_1-C_6)alkyl$, $(C_1-C_6)-alkyl-\overset{\overset{O}{\parallel}}{C}-NH-(C_1-C_6)alkyl$, $-\overset{\overset{O}{\parallel}}{C}NHCH$ and
 $-\overset{\overset{O}{\parallel}}{C}NH-(C_1-C_6)alkyl$; and wherein one of the phenyl moieties of
 45 said benzhydryl may optionally be replaced by naphthyl,
 thienyl, furyl or pyridyl;

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or R¹ and R², together with the nitrogen to which they are attached, form a saturated or unsaturated monocyclic ring containing from three to eight carbon atoms, a fused bicyclic ring containing from six to ten carbon atoms, or a saturated bridged ring system containing from six to ten carbon atoms;

R⁴ is aryl selected from phenyl and naphthyl; heteroaryl selected from indanyl, thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; and cycloalkyl having from three to seven carbon atoms wherein one of said carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; wherein each of said aryl and heteroaryl groups may optionally be substituted with one or more substituents, and said (C₃-C₇) cycloalkyl may optionally be substituted with one, two or three substituents, each of said substituents being independently selected from halo, nitro, (C₁-C₆) alkyl optionally substituted with from one to three fluorine atoms, (C₁-C₆) alkoxy optionally substituted with from one to three fluorine atoms, phenyl,

amino, (C₁-C₆) alkylamino, $\text{-}\overset{\text{O}}{\parallel}\text{C-NH-(C}_1\text{-C}_6\text{)alkyl}$, $\text{(C}_1\text{-C}_6\text{)alkyl-}\overset{\text{O}}{\parallel}\text{C-}$,

$\text{-}\overset{\text{O}}{\parallel}\text{C-O-(C}_1\text{-C}_6\text{)alkyl}$, $\text{-}\overset{\text{O}}{\parallel}\text{CH}$, $\text{-CH}_2\text{OR}^{12}$, $\text{NH}_2\text{(C}_1\text{-C}_6\text{)alkyl-}$,

$\text{-NH}\overset{\text{O}}{\parallel}\text{CH}$, $\text{-NH}\overset{\text{O}}{\parallel}\text{C-(C}_1\text{-C}_6\text{)alkyl}$, $\text{-NH-}\overset{\text{O}}{\parallel}\text{S-(C}_1\text{-C}_6\text{)alkyl}$ and

$\text{(C}_1\text{-C}_6\text{)alkyl-N-}\overset{\text{O}}{\parallel}\text{S-(C}_1\text{-C}_6\text{)alkyl}$;

R³ is hydrogen, (C₃-C₈)cycloalkyl, (C₁-C₆) straight or branched alkyl or phenyl optionally substituted with one or more substituents independently selected from halo, (C₁-

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C₆)alkyl optionally substituted with from one to three fluorine atoms, and (C₁-C₆)alkoxy optionally substituted with from one to three fluorine atoms;

R⁵ is hydrogen, (C₁-C₆)alkyl, or phenyl optionally substituted with one or more substituents independently selected from halo, (C₁-C₆)alkyl optionally substituted with from one to three fluorine atoms and (C₁-C₆)alkoxy optionally substituted with from one to three fluorine atoms;

R⁶ is selected from hydrogen, (C₁-C₆) straight or branched alkyl, (C₃-C₇) cycloalkyl wherein one of the carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; aryl selected from phenyl, biphenyl, indanyl and naphthyl; heteroaryl selected from thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; phenyl (C₂-C₆) alkyl, benzhydryl and benzyl, wherein each of said aryl and heteroaryl groups and the phenyl moieties of said benzyl, phenyl (C₂-C₆) alkyl and benzhydryl may optionally be substituted with one or more substituents independently selected from halo, nitro, (C₁-C₆) alkyl optionally substituted with from one to three fluorine atoms, (C₁-C₆) alkoxy, trifluoromethyl, amino, trihaloalkoxy

(e.g., trifluoromethoxy), (C₁-C₆)alkylamino, (C₁-C₆)alkyl-O-C(=O)-,

(C₁-C₆)alkyl-O-C(=O)-(C₁-C₆)alkyl, (C₁-C₆)alkyl-C(=O)-O-,

(C₁-C₆)alkyl-C(=O)-(C₁-C₆)alkyl-O-, (C₁-C₆)alkyl-C(=O)-,

(C₁-C₆)alkyl-C(=O)-(C₁-C₆)alkyl-, di-(C₁-C₆)alkylamino,

-C(=O)NH-(C₁-C₆)alkyl, (C₁-C₆)alkyl-C(=O)NH-(C₁-C₆)alkyl-, -NHCH(=O) and

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$\begin{array}{c} \text{O} \\ \parallel \\ \text{-NHC-} \end{array}$ -(C₁-C₆)alkyl; and wherein one of the phenyl moieties of said benzhydryl may optionally be replaced by naphthyl, thienyl, furyl or pyridyl; and

R¹² is hydrogen, (C₁-C₃)alkyl or phenyl;

or a pharmaceutically acceptable salt of such compound.

2. A compound according to claim 1, wherein one of R¹ and R² is hydrogen.

10 3. A compound according to claim 1, wherein R² is hydrogen, or R² and R¹, together with the nitrogen to which they are attached, form a monocyclic ring containing five to seven carbon atoms; R³ is hydrogen, methyl or phenyl; R⁵ is hydrogen; R⁴ is phenyl or indanyl wherein said phenyl or
15 indanyl may optionally be substituted with from one to three substituents independently selected from halo, nitro, (C₁-C₆)alkyl optionally substituted with from one to three fluorine atoms, (C₁-C₆)alkoxy, trihaloalkoxy (e.g., trifluoromethoxy), (C₁-C₆)alkylamino, -C(O)NH-(C₁-C₆)alkyl,
20 (C₁-C₆)alkyl-C(O)-, -C(O)-O-(C₁-C₆)alkyl, -C(O)H, -CH₂OR¹³, -NH(C₁-C₆)alkyl, -NHC(O)H, -NHC(O)-(C₁-C₆)alkyl, -NHSO₂(C₁-C₆)alkyl, and (C₁-C₆)alkyl-N-SO₂-(C₁-C₆)alkyl; and R⁶ is phenyl.

4. A compound according to claim 3, wherein R³ is hydrogen or methyl.

25 5. A compound according to claim 4, wherein R³ is hydrogen.

6. A compound according to claim 1, wherein R¹ is alkyl, R⁶ is unsubstituted phenyl, R⁴ is a monosubstituted or disubstituted aryl group that is substituted at the C-2
30 position with an alkoxy group or substituted at the C-5 position with an alkyl, alkoxy or trihaloalkoxy group, or substituted in such manner at both the C-2 and C-5 positions, and each of R², R³ and R⁵ is hydrogen.

7. A compound according to claim 1, wherein said
35 compound is selected from:

1-N-cyclohexyl-1-phenyl-2-N'-[(2-methoxyphenyl)methyl]-
1,2-ethanediamine;

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- 1-N-cyclohexyl-1-phenyl-2-N'-[(2-methoxy-5-trifluoromethoxyphenyl)methyl]-1,2-ethanediamine;
- 1-N-pyrrolidyl-1-phenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine;
- 5 1-N-methyl-1-phenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine;
- 1-N-cyclopentyl-1-phenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine;
- 1-N-propyl-1-phenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine;
- 10 1-N-phenylmethyl-1-phenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine;
- 1-N-cyclooctyl-1-phenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine;
- 15 1-N-cyclobutyl-1-phenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine;
- 1-N-(2-adamantyl)-1-phenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine;
- 1-N-(1,1-dimethylethyl)-1-phenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine;
- 20 1-N-cyclopropyl-1-phenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine;
- 1-N-isopropyl-1-phenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine;
- 25 1-N-(1-phenylethyl)-1-phenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine;
- 1-N-(2-norbornyl)-1-phenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine;
- 1-N-cyclohexyl-1-phenyl-2-N'-[(2-methoxy-5-tert-butylphenyl)methyl]-1,2-ethanediamine;
- 30 1-N-cyclohexyl-1-phenyl-2-N'-[(2-methoxy-5-isopropylphenyl)methyl]-1,2-ethanediamine;
- 1-N-cyclohexyl-1-phenyl-2-N'-[(2-methoxy-4,5-dimethylphenyl)methyl]-1,2-ethanediamine; and
- 35 1-N-cyclohexyl-1-N-(6-hydroxyhexyl)-1-phenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine.

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8. A compound according to claim 1, wherein said compound is selected from:

- 1 - a m i n o - 1 - p h e n y l - 2 - [(2 - m e t h o x y)
phenylmethylamino]propane;
- 5 (1R',2S')-1-cyclohexylamino-1-phenyl-2-[(2-methoxy)-
phenylmethylamino]propane;
- 1-N-cyclohexyl-1-phenyl-2-N'-[(2-methoxy-5-
trifluoromethoxyphenyl)methyl]-1,2-ethanediamine;
- 1 - N - p h e n y l m e t h y l - 1 - p h e n y l - 2 - N ' - [(2 -
10 methoxyphenyl)methyl]-1,2-ethanediamine dihydrochloride;
- 1-N-phenyl-1-phenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-
ethanediamine dihydrochloride;
- 1 - N - (2 - a d a m a n t y l) - 1 - p h e n y l - 2 - N ' - [(2 -
methoxyphenyl)methyl]-1,2-ethanediamine dihydrochloride;
- 15 1 - N - (1 , 1 - d i m e t h y l e t h y l) - 1 - p h e n y l - 2 - N ' - [(2 -
methoxyphenyl)methyl]-1,2-ethanediamine dihydrochloride;
- 1 - N - c y c l o p r o p y l - 1 - p h e n y l - 2 - N ' - [(2 -
methoxyphenyl)methyl]-1,2-ethanediamine dihydrochloride;
- 1-N-isopropyl-1-phenyl-2-N'-[(2-methoxyphenyl)methyl]-
20 1,2-ethanediamine dihydrochloride;
- 1 - N - (1 - p h e n y l e t h y l) - 1 - p h e n y l - 2 - N ' - [(2 -
methoxyphenyl)methyl]-1,2-ethanediamine dihydrochloride;
- 1 - N - (2 - n o r b o r n y l) - 1 - p h e n y l - 2 - N ' - [(2 -
methoxyphenyl)methyl]-1,2-ethanediamine dihydrochloride;
- 25 1 - N - (2 - a z a - b i c y c l o [4 . 4 . 0] d e c a n e) - 1 - p h e n y l - 2 - N ' - [(2 -
methoxyphenyl)methyl]-1,2-ethanediamine dihydrochloride;
- 1,1-diphenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-
ethanediamine;
- 1,1-diphenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-
30 ethanediamine dihydrochloride;
- 1,1-diphenyl-2-N'-[(2,5-dimethoxyphenyl)methyl]-1,2-
ethanediamine;
- 1,1-diphenyl-2-N'-[(2,4-dimethoxyphenyl)methyl]-1,2-
ethanediamine dihydrochloride;
- 35 1 - N - c y c l o h e x y l - 1 - N - (6 - n - h e x a n o l) - 1 - p h e n y l - 2 - N ' - [(2 -
methoxyphenyl)methyl]-1,2-ethanediamine;

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- 1-N-cyclohexyl-1-N-(3-phenylpropyl)-1-phenyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine;
- 3,3-diphenyl-2-N-cyclopentyl-1-N'-[(2-methoxyphenyl)methyl]-1,2-propanediamine dihydrochloride;
- 5 1-N-(2-phenylethyl)-1-(3,4-methylenedioxyphenyl)-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine dihydrochloride;
- 1-N-cyclopentyl-1-(2-naphthyl)-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine dihydrochloride;
- 10 1-N-cyclohexyl-1-cyclohexyl-2-N'-[(2-methoxyphenyl)methyl]-1,2-ethanediamine dihydrochloride;
- (1R,S)-cycloheptylamino-1-phenyl-(2R,S)-[(2-methoxyphenyl)methylamino]propane;
- (1R,S)-amino-1-phenyl-(2R,S)-[(2-methoxyphenyl)methylamino]propane;
- 15 (1R,S)-(4-pyranylamino)-1-phenyl-(2R,S)-[(2-methoxyphenyl)methylamino]propane;
- (1R,S)-cyclohexylamino-1-phenyl-(2R,S)-[(2-methoxyphenyl)methylamino]propane;
- (1R,S)-cyclopentylamino-1-phenyl-(2R,S)-[(2-methoxyphenyl)methylamino]propane dihydrochloride;
- 20 (1R,S)-n-propylamino-1-phenyl-(2R,S)-[(2-methoxyphenyl)methylamino]propane;
- (1R,S)-cyclohexylamino-1-phenyl-(2S,R)-[(2-methoxyphenyl)methylamino]propane dihydrochloride;
- 25 (1R,S)-N-pyrrolidyl-1-phenyl-(2S,R)-[(2-methoxyphenyl)methylamino]propane dihydrochloride;
- (1R,S)-N-piperidyl-1-phenyl-(2S,R)-[(2-methoxyphenyl)methylamino]propane;
- (1R,S)-cyclopentylamino-1-phenyl-(2S,R)-[(2-methoxyphenyl)methylamino]propane;
- 30 (1R,S)-cyclooctylamino-1-phenyl-(2S,R)-[(2-methoxyphenyl)methylamino]propane dihydrochloride;
- (1R,S)-propylamino-1-phenyl-(2S,R)-[(2-methoxyphenyl)methylamino]propane;
- 35 (1R,S)-methylamino-1-phenyl-(2S,R)-[(2-methoxyphenyl)methylamino]-3-methoxypropane; and

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(1R, S) - amino - 1 - phenyl - (2S, R) - [(2 - methoxyphenyl)methylamino] - 3 - methoxypropane.

9. A pharmaceutical composition for treating or preventing a condition selected from the group consisting of inflammatory diseases, anxiety, colitis, depression or dysthymic disorders, psychosis, pain, allergies, chronic obstructive airways disease, hypersensitivity disorders, vasospastic diseases, fibrosing and collagen diseases, reflex sympathetic dystrophy, addiction disorders, stress related somatic disorders, peripheral neuropathy, neuralgia, neuropathological disorders, disorders related to immune enhancement or suppression and rheumatic diseases in a mammal, comprising an amount of a compound according to claim 1 effective in preventing or treating such condition and a pharmaceutically acceptable carrier.

10. A method of treating or preventing a condition selected from the group consisting of inflammatory diseases anxiety, colitis, depression or dysthymic disorders, psychosis, pain, allergies, chronic obstructive airways disease, hypersensitivity disorders, vasospastic diseases, fibrosing and collagen diseases, reflex sympathetic dystrophy, addiction disorders, stress related somatic disorders, peripheral neuropathy, neuralgia, neuropathological disorders, disorders related to immune enhancement or suppression and rheumatic diseases in a mammal, comprising administering to a mammal in need of such treatment or prevention an amount of a compound according to claim 1 effective in preventing or treating such condition.

11. A pharmaceutical composition for antagonizing the effects of substance P at its receptor site in a mammal, comprising a substance P receptor antagonizing effective amount of a compound according to claim 1 and a pharmaceutically acceptable carrier.

12. A method of antagonizing the effects of substance P at its receptor site in a mammal, comprising administering to said mammal a substance P receptor antagonizing effective amount of a compound according to claim 1.

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13. A pharmaceutical composition for treating or preventing a condition in a mammal, the treatment or prevention of which is effected or facilitated by a decrease in substance P mediated neurotransmission, comprising an amount of a compound according to claim 1 effective in antagonizing the effect of substance P at its receptor site and a pharmaceutically acceptable carrier.

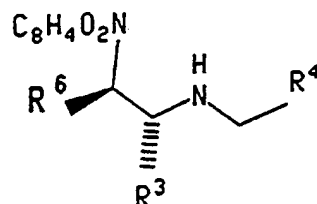
14. A method of treating or preventing a condition in a mammal, the treatment or prevention of which is effected or facilitated by a decrease in substance P mediated neurotransmission, comprising administering to a mammal in need of such treatment or prevention an amount of a compound according to claim 1, or a pharmaceutically acceptable salt thereof, effective in antagonizing the effect of substance P at its receptor site.

15. A pharmaceutical composition for treating or preventing a condition in a mammal, the treatment or prevention of which is effected or facilitated by a decrease in substance P mediated neurotransmission, comprising an amount of a compound according to claim 1, or a pharmaceutically acceptable salt thereof, effective in treating or preventing such condition and a pharmaceutically acceptable carrier.

16. A method of treating or preventing a condition in a mammal, the treatment or prevention of which is effected or facilitated by a decrease in substance P mediated neurotransmission, comprising administering to a mammal in need of such treatment or prevention an amount of a compound according to claim 1 effective in treating or preventing such condition.

17. A compound of the formula

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IX

wherein R^4 is aryl selected from phenyl and naphthyl; heteroaryl selected from indanyl, thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; and cycloalkyl having from three to seven carbon atoms wherein one of said carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; wherein each of said aryl and heteroaryl groups may optionally be substituted with one or more substituents, and said (C_3 - C_7) cycloalkyl may optionally be substituted with one, two or three substituents, each of said substituents being independently selected from halo, nitro, (C_1 - C_6) alkyl optionally substituted with from one to three fluorine atoms, (C_1 - C_6) alkoxy optionally substituted with from one to three fluorine atoms, phenyl, amino,

(C_1 - C_6) alkylamino, $\text{-}\overset{\text{O}}{\parallel}\text{C-NH-}(\text{C}_1\text{-C}_6)\text{alkyl}$, (C_1 - C_6) alkyl- $\overset{\text{O}}{\parallel}\text{C-}$,

$\text{-}\overset{\text{O}}{\parallel}\text{C-O-}(\text{C}_1\text{-C}_6)\text{alkyl}$, $\text{-}\overset{\text{O}}{\parallel}\text{CH-}$, $\text{-CH}_2\text{OR}^{12}$, $\text{NH}_2(\text{C}_1\text{-C}_6)\text{alkyl-}$,

$\text{-NH}\overset{\text{O}}{\parallel}\text{CH-}$, $\text{-NH}\overset{\text{O}}{\parallel}\text{C-}(\text{C}_1\text{-C}_6)\text{alkyl}$, $\text{-NH}\overset{\text{O}}{\parallel}\text{S-}(\text{C}_1\text{-C}_6)\text{alkyl}$ and

$(\text{C}_1\text{-C}_6)\text{alkyl-N-}\overset{\text{O}}{\parallel}\text{S-}(\text{C}_1\text{-C}_6)\text{alkyl}$;

R^3 is hydrogen, (C_3 - C_8) cycloalkyl, (C_1 - C_6) alkyl or phenyl optionally substituted with one or more substituents

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independently selected from halo, (C₁-C₆)alkyl optionally substituted with from one to three fluorine atoms, and (C₁-C₆)alkoxy optionally substituted with from one to three fluorine atoms; and

5 R⁶ is selected from hydrogen, (C₁-C₆) straight or branched alkyl, (C₃-C₇) cycloalkyl wherein one of the carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; aryl selected from phenyl, biphenyl, indanyl and naphthyl; heteroaryl selected from thienyl, furyl, pyridyl,
 10 thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; phenyl (C₂-C₆) alkyl, benzhydryl and benzyl, wherein each of said aryl and heteroaryl groups and the phenyl moieties of said benzyl, phenyl (C₂-C₆) alkyl and benzhydryl may optionally be substituted with one or more
 15 substituents independently selected from halo, nitro, (C₁-C₆) alkyl optionally substituted with from one to three fluorine atoms, (C₁-C₆) alkoxy, amino, trihaloalkoxy

20 (e.g., trifluoromethoxy), (C₁-C₆)alkylamino, (C₁-C₆)alkyl-O-C(=O)-,

25 (C₁-C₆)alkyl-O-C(=O)-(C₁-C₆)alkyl, (C₁-C₆)alkyl-C(=O)-O-,

(C₁-C₆)alkyl-C(=O)-, (C₁-C₆)alkyl-O-(C₁-C₆)alkyl-C(=O)-,

30 (C₁-C₆)alkyl-C(=O)-(C₁-C₆)alkyl-, di-(C₁-C₆)alkylamino,

35 -C(=O)NH-(C₁-C₆)alkyl, (C₁-C₆)alkyl-C(=O)NH-(C₁-C₆)alkyl-, -NHCH(=O) and

-NHC(=O)-(C₁-C₆)alkyl; and wherein one of the phenyl moieties of
 40 said benzhydryl may optionally be replaced by naphthyl, thienyl, furyl or pyridyl.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 92/07730

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC		
Int.Cl. 5 C07C217/58; C07D295/125; C07D209/48; A61K31/135 C07D295/12		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.Cl. 5	C07C ; C07D	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
X	FR,A,973 694 (SOCIÉTÉ DES USINES CHIMIQUES RHONE POULENC) 20 September 1950 see whole document ---	1-6
X	US,A,2 876 236 (SZABO ET. AL.) 3 March 1959 see column 9, line 70 - line 72 see column 10, line 6 - line 20; claims ---	1-6,9,10
X	US,A,2 634 293 (KYRIDES ET. AL.) 7 April 1953 see column 3, line 6 - line 11; claims ---	1-6
X	GB,A,1 173 833 (MILES LABORATORIES INC.) 10 December 1969 see page 1, line 51 - line 60; claims; examples --- -/-	1,3-6
<p>¹⁰ Special categories of cited documents :</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
17 DECEMBER 1992	13.01.93	
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE	HELPS I.M. <i>H.M. Helms</i>	

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	US,A,3 145 209 (KRAPCHO) 18 August 1964 see column 1, line 1-38 ---	1-6
X	US,A,3 975 443 (HARPER ET. AL.) 17 August 1976 see column 1, line 1 - line 39 ---	1-6,9,10
X	EP,A,0 135 087 (WELLCOME) 27 March 1985 see page 4, paragraph 2 - page 5, paragraph 1 see page 12, paragraph 1 ---	1-6
A	US,A,5 039 706 (WILKERSON) 13 August 1991 see claims; examples ---	1-10
A	FR,M,6 678 (SOCIÉTÉ ANONYME DES LABORATOIRES ROBERT ET CARRIÈRE) 3 February 1969 see whole document ---	1-10
A	GB,A,804 321 (FARMACEUTICI ITALIA S.A.) 12 November 1958 see whole document ---	1-10
A	EP,A,0 443 132 (FUJISAWA) 28 August 1991 see claims; examples -----	1-11,13, 15-17

INTERNATIONAL SEARCH REPORT

international application No.

PCT/US 92/07730

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 10, 12, 14 and 16 are drawn to a method of treatment of the human or animal body by therapy (Rule 39.1(iv)), the search has been carried out and based on the alleged effects of the claimed compounds.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Claims 1-6, 9-17 are so broadly formulated that they fail to meet the requirements of Article 6 PCT. The search has been restricted to the scope covered by Examples 1-46 (see Guidelines, B-111, 3-7)
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO. US 9207730
SA 64768**

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 17/12/92

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
FR-A-973694		None	
US-A-2876236		None	
US-A-2634293		None	
GB-A-1173833	10-12-69	BE-A- 702091 DE-A- 1695442 FR-A- 1535838 NL-A- 6710562	02-01-68 08-04-71 02-02-68
US-A-3145209		None	
US-A-3975443	17-08-76	US-A- 4049663 BE-A- 789025 CA-A- 995220 CH-A- 597153 DE-A- 2246728 FR-A,B 2154559 GB-A- 1410011 NL-A- 7212967	20-09-77 20-03-73 17-08-76 31-03-78 03-05-73 11-05-73 15-10-75 27-03-73
EP-A-0135087	27-03-85	DE-A- 3472252 JP-A- 60056957 US-A- 4590199	28-07-88 02-04-85 20-05-86
US-A-5039706	13-08-91	None	
FR-M-6678	03-02-69	None	
GB-A-804321		None	
EP-A-0443132	28-08-91	AU-A- 6801090 JP-A- 4210996	27-06-91 03-08-92